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Woodward et al.

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[54] **CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS**

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[73] Assignee: **Allergan**, Waco, Tex.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,607,978.

[21] Appl. No.: **605,567**

[22] Filed: **Feb. 22, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 371,339, Jan. 11, 1995, Pat. No. 5,607,978, which is a continuation of Ser. No. 154,244, Nov. 18, 1993, abandoned, which is a division of Ser. No. 948,056, Sep. 21, 1992, Pat. No. 5,352,708.

[51] **Int. Cl.**[6] **A61K 31/135**; A61K 31/44; A61K 31/38; A61K 31/34

[52] **U.S. Cl.** **514/357**; 514/438; 514/471; 514/514; 514/530; 514/548; 514/549; 514/551; 514/573; 514/613; 514/617; 514/659; 514/646; 514/729

[58] **Field of Search** 514/357, 530, 514/573, 613, 659, 729, 646, 438, 471, 514, 548, 549, 551, 617; 546/337; 560/121; 562/503, 504, 510; 564/189, 453, 454; 568/838

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[57] **ABSTRACT**

The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

20 Claims, No Drawings

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CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS

CROSSREFERENCE TO RELATED APPLICATIONS

This patent application is a continuation-in-part of U.S. patent application Ser. No. 08/371,339, filed on Jan. 11, 1995 now U.S. Pat. No. 5,607,978 which is a continuation of U.S. patent application Ser. No. 08/154,244 which was filed on Nov. 18, 1993, now abandoned, which is a divisional of U.S. patent application Ser. No. 07/948,056, filed on Sep. 21, 1992, now U.S. Pat. No. 5,352,708 issued on Oct. 4, 1994, all of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

2. Description of the Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors.

enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M. S. *Exp. Eye Res.* 1971, 11, pp. 170–177; Bito, L. Z. *Biological Protection with Prostaglandins* Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231–252; and Bito, L. Z., *Applied Pharmacology in the Medical Treatment of Glaucomas* Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477–505). Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the U.S. Pat. No. 4,599,353 certain prostaglandins, in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., *Invest. Ophthalmol. Vis. Sci.* 28 (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., *Arch. Ophthalmol.* 105, 1036 (1987), and Siebold et al., *Prodrug* 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending U.S. Ser. No. 386,835 (filed 27 Jul. 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the copending application U.S. Ser. No. 357,394 (filed 25 May 1989). Similarly, 11,15-9,15- and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications U.S. Ser. No. 385,645 filed 27 Jul. 1990, now U.S. Pat. No.

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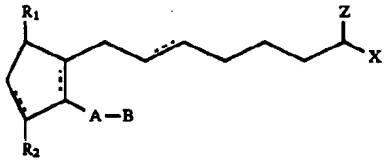
4,494,274; 584,370 which is a continuation of U.S. Ser. No. 386,312, and 585,284, now U.S. Pat. No. 5,034,413 which is a continuation of U.S. Ser. No. 386,834, where the parent applications were filed on 27 Jul. 1989. The disclosures of these patent applications are hereby expressly incorporated by reference.

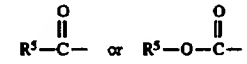
SUMMARY OF THE INVENTION

We have found that certain cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds and derivatives thereof wherein the carboxylic acid group is replaced by a non-acidic substituent have pronounced effects on smooth muscle and are potent ocular hypotensive agents. We have further found that such compounds, in certain instances, may be significantly more potent than their respective parent compounds and, in the case of glaucoma surprisingly, cause no or significantly lower ocular surface hyperemia than the parent compounds.

The present invention relates to methods of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive, allergic disease, shock and ocular hypertension which comprises administering an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I

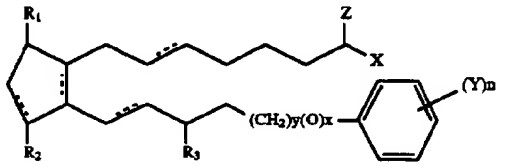


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or akylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



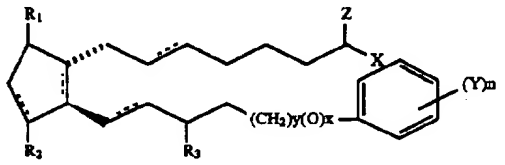
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R_1 and R_2 is =O, —OH or a —$O(CO)R_6$ group, and the other one is —OH or —$O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —$(CH_2)mR_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided, however, that when B is not substituted with a pendant heteroatom-containing radical, and Z is =O, then X is not —OR^4. (That is, the cycloalkyl or hydrocarbyl aryl or heteroaryl radical is not substituted with a pendant radical having an atom other than carbon or hydrogen.)

More preferably the method of the present invention comprises administering a cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) represented by the formula II



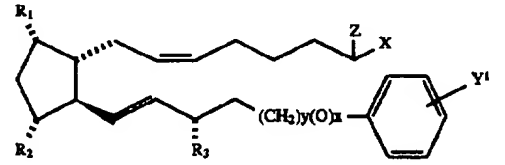
wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to about 3 and R_3 is =O, —OH or —$O(CO)R_6$ wherein R_6 is as defined above. Preferably, n is 1 or 2.

Preferably the compound used in the above method of treatment is a compound of formula (III).



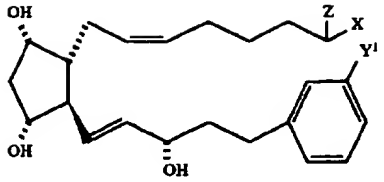
wherein hatched lines indicate a configuration, solid triangles are used to indicate β configuration

In another aspect, the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (IV)



wherein Y^1 is Cl or trifluoromethyl and the other symbols and substituents are as defined above, in combination with a pharmaceutical carrier.

Finally, the method of the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V



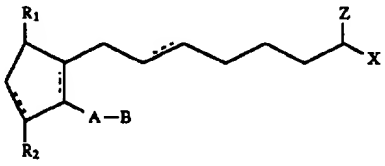
and the 9-and/or 11- and/or 15 esters thereof.

In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), (IV) or (V) wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

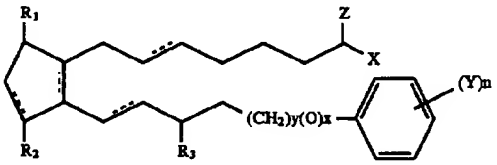
In a still further aspect, the present invention relates to cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds of the above formulae, wherein the substituents and symbols are as defined hereinabove, or a pharmaceutically acceptable salt of such compounds.

DETAILED DESCRIPTION OF THE INVENTION

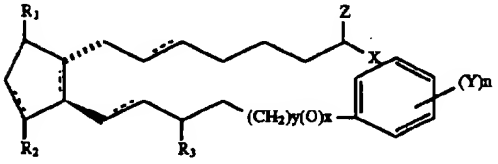
The present invention relates to the use of cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds as therapeutic agents, e.g. as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I,



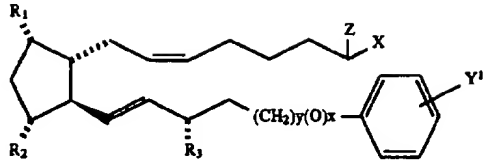
as defined above. The preferred nonacidic cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) compounds used in accordance with the present invention are encompassed by the following structural formula (II)



wherein the substituents and symbols are as hereinabove defined. More preferably the compounds are represented by formula (III).

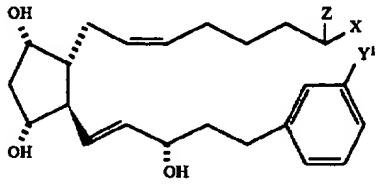


wherein the substituents and symbols are as defined above. More preferably, the compounds utilized in the present invention are compounds represented by the formula (IV)



wherein the substituents and the symbols are as defined above.

Most preferably the present invention utilizes the novel compounds of the formula (V)



and their 9- and/or 11- and/or 15-esters.

In all of the above formulae, as well as in those provided hereinafter, the dotted lines on bonds between carbons 5 and 6 (C-5), between carbons 13 and 14 (C-13), between carbons 8 and 12 (C-8), and between carbons 10 and 11 (C-10) indicate a single or a double bond which can be in the cis or trans configuration. If two solid lines are used that indicates a specific configuration for that double bond. Hatched lines at positions C-9, C-11 and C-15 indicate the α configuration. If one were to draw the β configuration, a solid triangular line would be used.

In the compounds used in accordance with the present invention, compounds having the C-9 or C-11 or C-15 substituents in the α or β configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cydopentane ring indicate substituents in the a configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the β configuration. Also, the broken line attachment of the hydroxyl group or other substituent to the C-11 and C-15 carbon atoms signifies the α configuration.

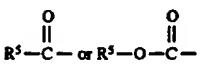
For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "saturated or unsaturated acydic hydrocarbon group" is used to refer to straight or branched chain, saturated or unsaturated hydrocarbon groups having from one to about 6, preferably one to about 4 carbon atoms. Such groups include alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl, e.g. methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof.

The definition of R_6 may include a cyclic component, $-(CH_2)_mR_7$, wherein n is 0 or an integer of from 1 to 10, R_7 is an aliphatic ring from about 3 to about 7 carbon atoms, or an aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or unsaturated, and preferably is a saturated ring having 3–7 carbon atoms, inclusive. As an aromatic ring, R_7 preferably is phenyl, and the heteroaromatic rings have oxygen, nitrogen or sulfur as a heteroatom, i.e. R_7 may be thienyl, furanyl, pyridyl, etc. Preferably m is 0 or an integer of from 1 to 4.

Z is =O or represents two hydrogen atoms.

X may be selected from the group consisting of $-OR^4$ and $-N(R^4)_2$ wherein R^4 is selected from the group con-

sisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



wherein R^5 is a lower alkyl radical having from one to six carbon atoms.

Preferred representatives of the compounds within the scope of the present invention are the compounds of formula V wherein X is —OH, i.e. cyclopentane heptenoic acid, 5-cis-2-(3-αhydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$ and cyclopentane methylheptenoate-5-cis-2(3-αhydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5 dihydroxy, $[1_{6\alpha},2_\beta,3_\alpha, 5_\alpha]$ and the 9- and/or 11- and/or 15-esters of this compound. (The numbered designations in brackets refer to the positions on the cydopentane ring.)

The following novel compounds may be used in the pharmaceutical compositions and the methods of treatment of the present invention.

(1) cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$.

(2) cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_{6\alpha}]$

(3) cydopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(4) cyclopentane heptenyl methoxide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(5) cyclopentane heptenyl ethoxide-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3. 5-dihydroxy, $[1_\alpha, 2_\beta, 3_\alpha,5_\alpha]$

(6) cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha, 2_\beta,3_\alpha, 5_\alpha]$

(7) cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-trifluoromethylphenoxy-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha, 2_\beta, 3_\alpha,5_\alpha]$

(8) cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(9) cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5 dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(10) cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(11) cyclopentane heptenol-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta3_\alpha, 5_\alpha]$

(12) cydopentane heptenamide-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3. 5-dihydroxy, $[1_\alpha, 2_\beta,3_\alpha,5_\alpha]$

(13) cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)3. 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Such salts are those formed with pharmaceutically acceptable cations, e.g., alkali metals, alkali earth metals, etc.

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonidty adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001–5
preservative	0–0.10
vehicle	0–40
tonicity adjustor	0–10
buffer	0.01–10
pH adjustor	q.s. pH 4.5–7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered

application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20–35 ml.

The invention is further illustrated by the following non-limiting Examples.

EXAMPLE 1

Cyclopentane heptenoic acid, 5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

EXAMPLE 2

Cyclopentane methylheptenoate-5-cis-2(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy; $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

To a stirred solution of cyclopentane heptenoic acid, 5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$(24 mg. 0.0565 mmol) in acetone (0.6 ml) at room temperature was added 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) (40. ul, 0.27 mmol) and methyl iodide (20 ul, 0.32 mmol). The reaction turned yellow with the DBU addition. The reaction was maintained at room temperature for 6.5 hours, then was diluted with ethyl acetate (30 ml) and filtered through a plug of celite with the aid of ethyl acetate. After concentration in vacuo, the residue was flushed with ethylacetate (EtOAc) through a 20 mm×160 mm column of silica to give the desired methyl ester.

EXAMPLE 3

Cyclopentane heptenamide-5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

A mixture of the methyl ester of the compound of Example 1 (9.2 mg, 0.0222 mmol) and NH_4Cl (10 mg, 0.187 mmol) in NH_3 was heated at 80° C. for 12 hours. After cooling to room temperature, the solvents were evaporated and the residue was subjected to column chromatography to provide the named amide as 7.2 mg of a clear, colorless liquid.

EXAMPLE 4

Cyclopentane heptenoic acid-5-cis-2-(3α-hydroxyl-4-m-trifluoromethylphenoxy-1-trans-butenyl)-3,5-dihydroxy $[1\alpha.2\beta.3\alpha.5\alpha]$

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

EXAMPLE 5

Cyclopentane heptenamide-5-cis-2-(3α-hydroxyl-4-m-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy $[1\alpha.2\beta.3\alpha.5\alpha]$

A mixture of the methyl ester of the compound of Example 4 (fluprostenol) and NH_4Cl in NH_3 is heated at 80° C. for 12 hours. After cooling to room temperature the solvents are evaporated and the residue is subjected to column chromatography to provide the named amide.

EXAMPLE 6

Measurement of intraocular pressure studies in dogs involved pneumatonometry performed in conscious, Beagle dogs of both sexes (10–15 kg). The animals remained conscious throughout the study and were gently restrained by hand. Drugs were administered topically to one eye as a 25 μL volume drop, the other eye received 25 μL vehicle (0.1% polysorbate 80:10 mM TRIS) as a control. 0.1% proparacaine was used for corneal anesthesia during tonometry. Intraocular pressure was determined just before drug administration and at 2, 4 and 6 hours thereafter on each day of the 5 day study. Drug was administered twice a day, with a 6 hour interval between doses that spanned the intraocular pressure measurement time frame. The result reported in Table 1, below.

TABLE 1

Comparison of effects of certain compounds of the invention on dog intraocular pressure. Values indicate mean changes from baseline intraocular pressure (±SEM) at predetermined times post-dosing. n = 8, *p < 0.05, **p < 0.01.

		INTRAOCULAR PRESSURE (mmHg) CHANGE AT PREDETERMINED TIMES (HR)			
COMPOUND	DOSE %	2	4	6	24
Example 1	0.01	−0.1 ± 0.8	−5.2 ± 1.4**	−4.3 ± 0.8	−4.4 ± 0.8
Example 1	0.1	−3.1 ± 0.8**	−3.2 ± 0.7	−2.7 ± 0.8	—
Example 3	0.01	−2.2 ± 1.0*	5.5 ± 1.1**	−4.0 ± 1.4*	2.7 ± 1.1*
Example 3	0.1	−1.3 ± 0.4*	2.3 ± 0.7**	−2.6 ± 0.6**	—
Example 5	0.1	−2.7 ± 0.8*	−3.4 ± 0.9*	−2.8 ± 0.4**	−2.1 ± 1.6*
Example 4	0.01	−0.9 ± 0.7	−2.5 ± 0.7*	−3.2 ± 0.7**	−1.3 ± 0.7
Fluprostenol	0.1	−1.3 ± 0.1	−2.1 ± 1.1	−2.7 ± 1.3	−3.1 ± 0.9*

EXAMPLE 7

Measurement of ocular surface hyperemia was visually assessed and scored according to the following schematic:

Hyperemia Score	Assigned Value
<1	1
1 slight	2
>1 < 2	3
2 moderate	4

-continued

Hyperemia Score	Assigned Value
>2 > 3	5
3 severe	6

(baseline scores for dogs are typically < 1)

The hyperemia value for each dog at a single time point (x) is obtained as follows: (treated eye value at hr x-baseline value)-(control eye value at hr x-baseline value). A composite value is then obtained by dividing the sum of the post-treatment measurement at each time point by the number of animals in the group: i.e. m where m=n measurements of ocular surface hyperemia. Ocular surface hyperemia is evaluated at the same time points as intraocular pressure measurement. It should be noted that untreated dog eyes frequently have a pink/red tone. Thus, values of <1 and 1 are essentially within the normal range. The results are reported in Table 2, below.

TABLE 2

Comparison of effects of certain compounds of the invention on dog ocular suface hyperemia. Values are composite scores as indicated in the methods.

COMPOUND	DOSE %	OCULAR SURFACE HYPEREMIA: COMPOSITE SCORE
Example 1	0.01	—
Example 1	0.1	0.33
Example 3	0.01	—
Example 3	0.1	0.81
Example 5	0.1	0.81
Example 4	0.01	1.08
Fluprostenol	0.1	1.50

It is clear that the compounds of Examples 1, 3 and 5, unexpectedly, show better efficacy at lowering IOP than Example 4 while showing less hyperemia.

The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heat failure, and angina pectoris, in which case the compounds may be administered by any means that effect vasodilation and thereby relieve the symptoms of the disease. For example, administration may be by oral, transdermal, parenterial, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

The compounds of the invention may be used alone, or in combination with other of the known vasodilator drugs.

The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and petroatum and lanolin alcohol. Other suitable bases will be readily apparent to those skilled in the art.

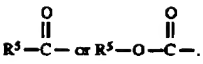
The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or caldum phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as inders such as starch, paste using for example, maize starch, wheat starch, rich starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable formulations for intravenous or parenteral administration include aqueous solutions of the active compounds. In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, soribitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

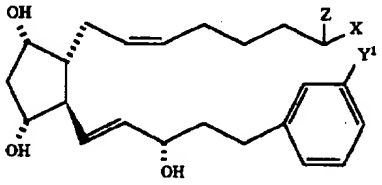
The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. For example, the present invention contemplates certain prodrugs of the above disclosed compounds, wherein R^4 is



These compounds may be made by acylation or esterification of the corresponding hydroxy or amino derivative. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

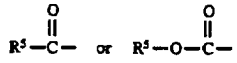
We claim:

1. A method of treating ocular hypertension or glaucoma which comprises applying to the eye an amount sufficient to treat ocular hypertension or glaucoma of a compound represented by the formula V



V

wherein X is a radical selected from the group consisting —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



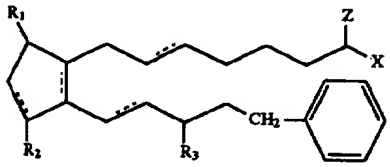
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; Y' is Cl or trifluoromethyl and the 9- and/or 11- and/or 15 esters, thereof.

2. The method of claim 1 wherein Z is =O and X is selected from the group consisting of NH_2.

3. The method of claim 1 wherein Z is =O and X is selected from the group consisting of amido radicals.

4. The method of claim 1 wherein X is selected from the group consisting of NH_2 and OCH_3.

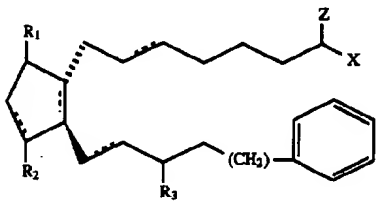
5. A method of treating ocular hypertension or glaucoma which comprises applying to the eye an amount sufficient to treat ocular hypertension or glaucoma of the formula



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, X is a radical selected from the group consisting of —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting or hydrogen, a lower alkyl radical having from one to six carbon atoms,

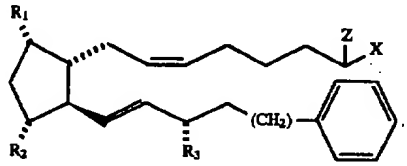
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; R_3 is =O, —OH or —$O(CO)R_6$; one of R_1 and R_2 is =O, —OH or a —$O(CO)R_6$ group, and the other one is —OH or —$O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —$(CH_2)_mR_7$ wherein m is 0–10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; or a pharmaceutically-acceptable salt thereof, provided however that when Z is =O, then X is not —OR^4.

6. The method of claim 5 wherein said compound is represented by the formula

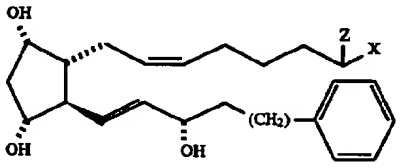


wherein hatched lines indicate the α configuration and solid triangles indicate the β configuration.

7. The method of claim 6 wherein said compound is represented by the formula



8. The method of claim 7 wherein said compound is represented by the formula



and the 9- and/or 11- and/or 15 esters, thereof.

9. The method of claim 8 wherein Z is =O and X is —$N(R^4)_2$.

10. The method of claim 9 wherein said compound is selected from the group consisting of

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_α,2_β,3_α,5_α];

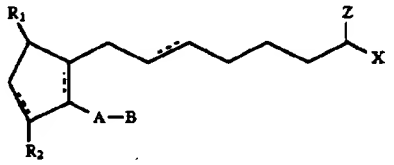
cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]; and

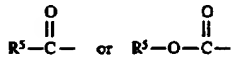
cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α].

11. A method of treating cardiovascular pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases and shock in a human which comprises administering to said human an effective amount of a compound of formula I



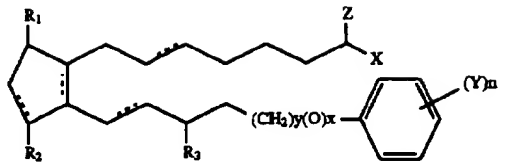
(I)

wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms, or an aryl radical selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting or hydrogen, a lower alkyl radical having from one to six carbon atoms,



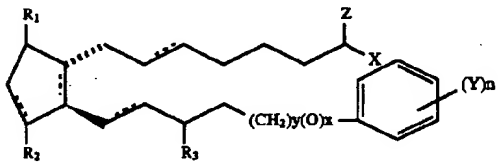
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R_1 and R_2 is =O, —OH or a —$O(CO)R_6$ group, and the other one is —OH or —$O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —$(CH_2)_mR_7$ wherein m is 0–10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that when B is not substituted with a pendant heteroatom-containing radical and Z is =O, then X is not —OR^4.

12. The method of claim 11 wherein said compound represented by the formula (II)



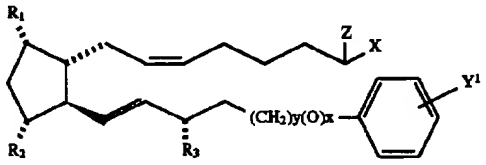
wherein y is 0 or 1, x is 0 or 1 and x+y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy,. alkyloxy, alkylcarboxy and halosubstituted alkyl, wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to 3 and R_3 is =O, —OH or —$O(CO)R_6$.

13. The method of claim 12 wherein said compound is represented by formula III.



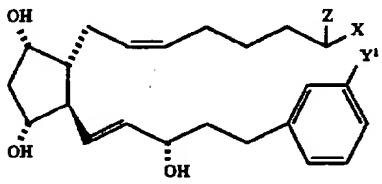
wherein hatched lines indicate the α configuration and solid triangles indicate the β configuration.

14. The method of claim 13 wherein said compound is represented by the formula IV.



wherein Y^1 is Cl or trifluoromethyl.

15. The method of claim 14 wherein said compound is a represented by the formula V



and the 9- and/or 11- and/or 15 esters, thereof.

16. The method of claim 15 wherein Z is =O and X is selected from the group consisting of NH_2 or OCH_3.

17. The method of claim 15 wherein Y^1 is Cl or trifluoromethyl, Z is =O and X is selected from the group consisting of alkoxy and amido radicals.

18. The method of claim 11 wherein said compound is selected from the group consisting of:

cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenyl methoxide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenyl ethoxide-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenol-5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α] and

cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenylpentyl)3, 5-dihydroxy, [1_α,2_β,3_α,5_α].

19. The method of claim **17** wherein X is selected from the group consisting of NH_2 and OCH_3.

20. The method of claim **11** wherein said compound is selected from the group consisting of:

cyclopentane heptenoic acid-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]; and

cyclopentane heptenonic acid-5-cis-2-(3α-hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α].

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,688,819

DATED : November 18, 1997

INVENTOR(S) : Woodward et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below: On the title page: Item [54] and Column 1, line 1,

Insert —NON-ACIDIC— before "CYCLOPENTANE"

Column 6, line 38; delete "cydopentane" and insert in place thereof —cyclopentane—

Column 6, line 39; delete "a" and insert in place thereof —α—

Column 7, line 15; delete "1_{60}" and insert in place thereof —1α—

Column 7, line 18; delete "cydopentane" and insert in place thereof —cyclopentane—

Column 7, line 25; delete "$5_{6}\alpha$" and insert in place thereof —5α—

Column 7, line 26; delete "cydopentane" and insert in place thereof —cyclopentane—

Column 8, line 29; delete "tonidty" and insert in place thereof —tonicity—

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,688,819

DATED : November 18, 1997

INVENTOR(S) : Woodward et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, line 16; delete "1_a,2_b,3_a,5_a" and insert in place thereof
--1_α, 2_β, 3_α,5_α--

Signed and Sealed this

Eighth Day of December, 1998

Bruce Lehman

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

United States Patent [19]

Vorbrueggen et al.

[11] **4,217,360**

[45] **Aug. 12, 1980**

[54] **NOVEL 1,3-BENZODIOXANEPROSTANOIC ACID DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF**

[75] Inventors: **Helmut Vorbrueggen; Norbert Schwarz; Olaf Loge; Walter Elger,** all of Berlin, Fed. Rep. of Germany

[73] Assignee: **Schering Aktiengesellschaft,** Berlin & Bergkamen, Fed. Rep. of Germany

[21] Appl. No.: **2,268**

[22] Filed: **Jan. 10, 1979**

Related U.S. Application Data

[63] Continuation of Ser. No. 888,059, Mar. 20, 1978, abandoned, which is a continuation of Ser. No. 800,126, May 24, 1977, abandoned, which is a continuation of Ser. No. 659,130, Feb. 18, 1976, abandoned.

[30] **Foreign Application Priority Data**

Feb. 27, 1975 [DE] Fed. Rep. of Germany 2508826

[51] **Int. Cl.**[2] **C07D 319/08**

[52] **U.S. Cl.** **424/278;** 260/340.3; 542/426; 542/429; 542/430

[58] **Field of Search** 542/429, 426, 430; 260/340.3, 340.7; 424/278

[56] **References Cited**

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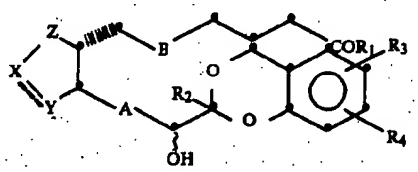
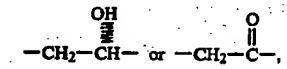
Primary Examiner—Arthur P. Demers
Attorney, Agent, or Firm—Millen & White

[57] **ABSTRACT**

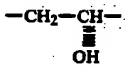
1,3-Benzodioxaneprostanoic acid compound of the formula



wherein R_1 is hydroxy, alkoxy of 1-10 carbon atoms, methylsulfamido, substituted or unsubstituted aryloxy, or O—CH_2—U—V wherein U is a direct bond, carbonyl, or carbonyloxy, and V is phenyl or phenyl substituted, e.g. by one or more of phenyl, phenoxy, alkoxy of 1-2 carbon atoms, and halogen; A is —CH_2—CH_2— or trans —CH=CH—; B is —CH_2—CH_2— or cis- or trans—CH=CH—; Z is hydroxymethylene or carbonyl; X------Y, if Z is hydroxymethylene, is



or, if Z is carbonyl, is



or —CH=CH—; R_2 is hydrogen or alkyl of 1-5 carbon atoms; R_3 and R_4 each are H, F, Cl, Br, I or CF_3, CH_3 or alkoxy of 1-2 carbon atoms or R_3 and R_4 in 6-,7-position is methylendioxy; and if R_1 is hydroxy, salts thereof with pharmaceutically acceptable bases, are agents for inducing menstruation, interrupting pregnancy, inducing labor and synchronizing the sexual cycle in female mammals.

76 Claims, No Drawings

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NOVEL 1,3-BENZODIOXANEPROSTANOIC ACID DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

This is a continuation or application Ser. No. 888,059, filed on Mar. 20, 1978, now abandoned, which is a continuation of Ser. No. 800,126, filed on May 24, 1977, now abandoned, which in turn is a continuation of Ser. No. 659,130, filed on Feb. 18, 1976, now abandoned.

BACKGROUND OF THE INVENTION

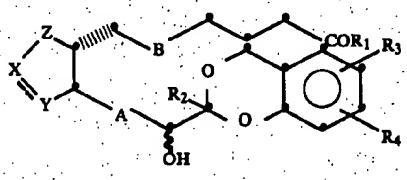
The various effects of prostaglandins in mammalian organisms, as well as in vitro, are of brief duration, since the prostaglandins are rapidly converted to pharmacologically inactive metabolic products. For example, an inactive metabolite is formed by oxidation of the allylic hydroxy function at the 15 carbon atom by 15-hydroxyprostaglandin dehydrogenases.

Therefore, the need to develop prostaglandin analogs which have a spectrum of activity comparable to that of natural prostaglandins, but longer duration and selectivity of activity, has been apparent.

1,3-Benzodioxaneprostaglandins surprisingly show a longer duration of activity, a higher selectivity and a higher effectiveness than naturally occurring protaglandins.

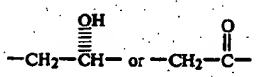
SUMMARY OF THE INVENTION

In a compositional aspect, this invention relates to 1,3-benzodioxaneprostanoic acid compounds of Formula I

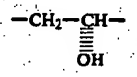


I

wherein R_1 is hydroxy; alkoxy of 1-10 carbon atoms; methylsulfamido; substituted or unsubstituted aryloxy; or O—CH_2—U—V, wherein U is a direct bond, carbonyl, or carbonyloxy, and V is phenyl or phenyl substituted, e.g. by one or more phenyl, phenox alkoxy of 1-2 carbon atoms or halogen. A is —CH_2—CH_2— or trans—CH=CH—; B is —CH_2—CH_2— or cis- or trans—CH=CH—; Z is hydroxymethylene or carbonyl. X ═══Y, when Z is hydroxymethylene, is



or, when Z is carbonyl, is



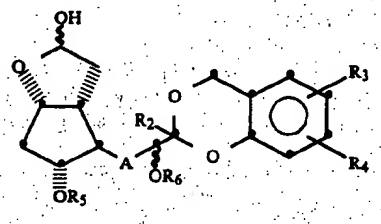
or —CH=CH—; R_2 is hydrogen or alkyl of 1-5 carbon atoms; R_3 and R_4 are alike or different and each is H, F, Cl, Br, I, CF_3, CH_3, or alkoxy of 1-2 carbon atoms or R_3 and R_4 in 6-,7-position is methylenedioxy; and when R_1 is hydroxy, salts thereof with pharmaceutically acceptable bases, including both the optical antipodes and racemates thereof.

In another compositional aspect, this invention relates to novel lactol intermediates of Formula II hereinafter.

In another compositional aspect, this invention relates to a pharmaceutical composition for inducing menstruation, interrupting pregnancy, inducing labor or synchronizing the sexual cycle in female mammals, comprising a compound of Formula I or a salt thereof with a pharmaceutically acceptable carrier, in admixture with a pharmaceutically acceptable carrier

In another aspect, this invention relates to methods of using a compound of Formula I or a salt thereof with a pharmaceutically acceptable carrier for interrupting pregnancy or inducing labor in a pregnant female mammal or synchronizing the sexual cycle of a sexually mature female mammal.

In another aspect, this invention relates to a process for preparing 1,3-benzodiaxaneprostanoic acids of Formula I, comprising reacting a lactol of Formula II



II

wherein R_2, R_3, R_4, and A are as above and R_5 and R_6 each are hydrogen or a hydroxy blocking group, with a Wittig reagent of Formula III

$$Ph_3P{=}CH{-}(CH_2)_3{-}COR_1 \qquad \text{III}$$

wherein Ph is phenyl and R_1 is as above;

and, optionally after oxidation of the 9-hydroxy group cleaving of any remaining hydroxy blocking groups;

and, in any desired sequence, esterifying a free 1-carboxy; saponifying an esterified 1-carboxy group; and/or reducing a 9-keto group and/or hydrogenating a 5,6-double bond; and/or hydrogenating a 13,14- and 5,6-double bond; and/or dehydrating a 9-keto compound and eliminating an 11-hydroxy; and or blocking the 11- and 15-hydroxy and oxidizing the 9-hydroxy; and/or blocking the 9- and 15-hydroxy groups and oxidizing the 11-hydroxy; and converting a 1-carboxy compound with a base to a pharmaceutically acceptable salt and/or separating the reacemates thereof.

DETAILED DESCRIPTION

Substituted or unsubstituted R_1 aryloxy groups include phenoxy, 1-naphthoxy and 2-naphthoxy, each of which can be mono-, di- or poly-substituted, e.g., by 1-3 halogen atoms, phenyl, phenoxy, 1-3 alkyl or alkoxy of 1-4 carbon atoms, one each of chloromethyl, fluoromethyl, trifluoromethyl, carboxy and hydroxy. Preferred are chloro, bromo, trifluoromethyl, phenyl, phenoxy, methoxy.

R_1 alkoxy groups include straight- and branched-chain, saturated and unsaturated alkoxy of 1-10 carbon atoms. Saturated alkoxy of 1-6 carbon atoms are preferred. Examples of R_1 alkoxy include methoxy, ethoxy, propoxy, butoxy, isobutoxy, tert.-butoxy pentoxy, hexoxy, heptoxy, octoxy, butenyloxy, isobutenyloxy, propenyloxy.

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R_1 can also be methylsulfamido, i.e., CH_3SO_2NH—, or —O—CH_2—U—V, i.e., —O—CH_2—V, —O—CH_2CO—V and —O—CH_2COO—V wherein V is, e.g., p-Cl-phenyl, p-F-phenyl, p-Br-phenyl, phenyl, m-methoxyphenyl, p-phenylphenyl, p-phenoxyphenyl.

Examples of R_2 alkyl groups of 1-5 carbon atoms are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and pentyl.

Any inorganic or organic base known to those skilled in the art for the production of physiologically compatible salts can be employed. Examples are alkali metal hydroxides, such as sodium or potassium hydroxide; alkaline earth hydroxides, such as calcium hydroxide; ammonia; amines, such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, and tris(hydroxymethyl)-methylamine, etc.

Compounds of Formula I which are preferred incorporate one or more of the preferred functions of R_1, A, B, Z, X═══Y, R_2, R_3 or R_4, include the following compounds, which otherwise correspond to Formula I, but wherein:

(a) A is —CH_2CH_2—;

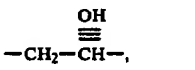
(b) A is trans- —CH═CH—;

(c) B is —CH_2CH_2—, including each of (a)-(b);

(d) B is cis- —CH═CH—, including each of (a)-(b);

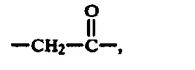
(e) B is trans- —CH═CH—, including each of (a)-(b);

(f) Z is hydroxymethylene and X═══Y is



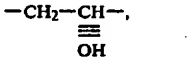
including each of (a)-(e);

(g) Z is hydroxymethylene and X═══Y is



including each of (a)-(e);

(h) Z is carbonyl and X═══Y is



including each of (a)-(e);

(i) Z is carbonyl and X═══Y is —CH═CH—, including each of (a)-(e);

(j) R_1 is hydroxy, including each of (a)-(i);

(k) R_1 is alkoxy of 1-10 carbon atoms, including each of (a)-(i);

(l) R_1 is methoxy and R_3 and R_4 are H, including each of (a)-(i); and

(m) R_1 is p-phenylphenacyloxy and R_3 and R_4 are H, including each of (a)-(i).

Reaction of lactols II with a Wittig reagent of Formula III, produced from the corresponding phosphonium bromide and methanesulfinylmethylsodium or potassium tert.-butylate in the usual way in dimethyl sulfoxide, is accomplished at temperatures of 0°-100° C., preferably at 20°-80° C., in an aprotic solvent, preferably dimethyl sulfoxide or dimethylformamide. The Wittig reagent can also be liberated by reaction of 4—R_1—CO—triphenylbutylphosphonium bromide with potassium tert.-butylate.

Oxidation of the 9-hydroxy group to the ketone, which can take place before splitting off the hydroxy blocking groups, is effected with the customary oxidizing agents, e.g., with Jones reagent (J. Chem. Soc. 1953, 2555). The reaction is conducted in an excess of the oxidizing agent in a suitable diluent, such as acetone, at temperatures of between 0° C., and −50° C., preferably at −20° C. The reaction is generally finished after 5-30 minutes.

The oxidation of the 9-hydroxy group takes place preferably after first blocking the 11- and 15-hydroxy groups, e.g., by silylation (Chem. Comm. [1972], 1120). Other usable oxidizing agents are silver carbonate on "Celite" or mixtures of chromium trioxide and pyridine (Tetrahedron Letters 1968, 3363).

The 11-hydroxy group is oxidized by the usual oxidizing agents, e.g, with Jones reagent or Collins reagent, after first blocking the 9- and 15-hydroxy groups. This reaction is carried out at temperatures of between −40° C. and +20° C., preferably at −20° C.

Suitable hydroxy blocking groups R_5 and R_6 are known to those skilled in the art, preferably cyclic α,β-unsaturated ethers, for example, dihydropyran, dihydrofuran, and α-ethoxyethylene; and acyl residues, e.g., aromatic and aliphatic organic acid groups, preferably benzoyl and acetyl.

OH blocking groups, e.g., THP and THF ethers, are removed to obtain compounds of Formula I by conventional methods in an aqueous solution of an organic acid, for example, acetic acid, propionic acid, etc., or in an aqueous solution of an inorganic acid, e.g., hydrochloric acid. To improve solubility, a water-miscible inert organic solvent is advantageously added. Suitable organic solvents are alcohols, such as methanol and ethanol, and ethers, such as dimethoxyethane, dioxane, and tetrahydrofuran. Tetrahydrofuran is preferably employed. The hydrolysis is executed preferably at temperatures of between 20° C. and 80° C. In case of compounds of the prostaglandin E type, the hydrolysis is conducted at below 45° C. to avoid the formation of prostaglandin A compounds as by-products.

The acyl groups are split off with alkali metal carbonates, e.g., potassium carbonate in methanol at 0°-50° C., preferably at 25° C.

Reduction of the 9-oxo group to obtain a mixture of epimeric 9-α- and 9-β-alcohols is conducted in the usual way, preferably in an organic solvent with sodium borohydride or zinc borohydride. If zinc borohydride is used, suitable solvents include dimethoxyethane, diethyl ether, dioxane, benzene and isopropyl ether. When using sodium borohydride, solvents which can be used are methanol, ethanol, isopropanol and n-propanol. The thus-formed mixture of epimers is separated by column or layer chromatography and/or fractional crystallization.

Dehydration of the 9-oxo compound, wherein the 11-hydroxy group and a hydrogen atom for the 10-position are split off, to form a prostaglandin A derivative can be conducted under conditions generally known to a person skilled in the art. In general, the dehydration is effected in a solution of an organic acid, such as acetic acid, or an inorganic acid, such as hydrochloric acid, at temperatures of between 20° C. and 80° C. The reaction is terminated after about 2 to 17 hours.

The hydrogenation of the 13,14- and/or 5,6-double bond is accomplished in a hydrogen atmosphere and in the presence of a noble metal catalyst. A suitable catalyst is, for instance, 10% palladium on charcoal. If the hydrogenation is conducted at room temperature, the

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5,6- and 13,14-double bonds can be saturated. At low temperatures, preferably at −80° C. to −10° C., the cis-5,6-double bond can be hydrogenated before the trans-13,14-double bond. Selective reduction of the cis-5,6-double bond in a compound with a trans-13,14-double bond is also effected using nickel boride or tris(-triphenylphosphine)rhodium(I) chloride as catalyst.

In order to prepare the esters of Formula I wherein R_1 is alkoxy of 1-10 carbon atoms, the 1-carboxy compounds are reacted conventionally with diazohydrocarbons. The esterification with diazo-hydrocarbons takes place by mixing a solution of the diazo-hydrocarbon in an inert solvent, preferably in diethyl ether, with the 1-carboxy compound in the same inert solvent or in another inert solvent, e.g., methylene chloride. After the reaction is finished (within 1-30 minutes), the solvent is removed and the ester purified in the usual manner.

Diazoalkanes are either known or can be prepared in accordance with conventional methods. Org. Reactions 8: 389-394 (1954).

To introduce the ester group $O—CH_2—U—V—$ for R_1, a 1-carboxy compound of Formula I is reacted, in the presence of a hydrogen halide acceptor, with a halogen compound of the formula

$$Hal—CH_2—U—V,$$

wherein Hal is halogen, preferably bromine; U is a direct bond, a carbonyl or carbonyloxy, and V is phenyl or phenyl substituted e.g. by one ore more phenyl, phenoxy, alkoxy of 1-2 carbon atoms or halogen, preferably bromine.

Suitable hydrogen halide acceptors include silver oxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, or amines, such as trimethylamine, triethyamine, tributylamine, trioctylamine, and pyridine. The reaction with the halogen compound is accomplished in an inert solvent, preferably in acetone, acetonitrile, dimethylacetamide, dimethylformamide, or dimethyl sulfoxide at temperatures of −80° C. to +100° C., preferably at room temperature.

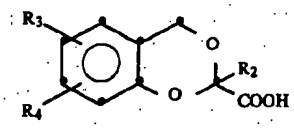
In order to prepare esters of Formula I wherein R_1 is a substituted or unsubstituted aryloxy group, the 1-carboxy compounds are reacted with the corresponding arylhydroxy compounds and dicyclohexylcarbodiimide in the presence of a suitable base, e.g., pyridine or triethylamine, in an inert solvent. Suitable solvents are methylene chloride, ethylene chloride, chloroform, ethyl acetate, tetrahydrofuran, preferably chloroform. The reaction is conducted at temperatures of between −30° C. and +50° C., preferably at 10° C.

The saponification of the prostaglandin esters takes place according to the methods known to those skilled in the art; for example, with potassium hydroxide in methanol.

The prostaglandin derivatives of Formula I wherein R_1 is hydroxy can be converted into salts by neutralization with equivalent amounts of the corresponding inorganic bases. For example, the corresponding PG acid is dissolved in water containing the stoichiometric quantity of the base. The solid inorganic salt is obtained after evaporation of the water and after adding a water-miscible solvent, e.g., alcohol or acetone.

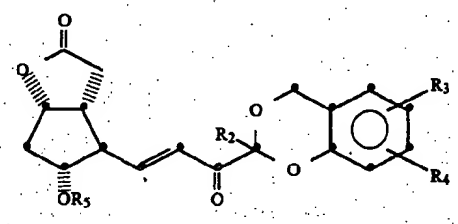
To produce an amine salt, the PG acid is dissolved in a suitable solvent, e.g., ethanol, acetone, diethyl ether, or benzene, and at least a stoichiometric amount of the amine is added to the solution. The salt is ordinarily obtained as a solid.

The lactols of Formula II serving as the starting compounds can be produced by reacting 2-hydroxy-methylphenols (saligenins) with dihalocarboxylic acids to give 1,3-benzodioxane 2-carboxylic acids of Formula IV



IV

The thus-obtained 1,3-benzodioxane-2-carboxylic acid is present as the racemate because of the asymmetrical carbon atom in the 2-position. The racemate can be separated by salt formation with optically active bases into the optical antipodes. The subsequent esterification can be conducted with the racemate and/or with the enantiomer. The thus-obtained 1,3-benzodioxane-2-carboxylic acid ester is reacted with triphenylphosphine methylene or a methylphosphonic acid dialkyl ester. From the product, a ketone of Formula V below is then prepared in a conventional manner by a Wittig and/or a Wittig-Horner reaction with an aldehyde (preferably in the form of the corresponding antipode)



V

The C_{16}-diastereomer mixture which may thus have been produced can be separated according to the usual methods.

In the presence of noble metal salt catalysts, the keto of general Formula V can be hydrogenated, if desired, in the 13,14-position (PG numbering) in an inert solvent.

The subsequently conducted reduction to the α- and β-C_{15}-alcohols takes place with sodium borohydride or zinc borohydride. The mixture of epimers can be separated according to the customarily known methods. After the introduction of hydroxy blocking groups, such as, for example, dihydropyran, in position 15 and optionally in position 11 (PG numbering), the lactone is reduced to the desired lactol of general Formula II with diisobutylaluminum hydride and/or lithim tri-tert.-butoxyaluminum hydride.

The reduction to the lactol of general Formula II can also be conducted without blocking groups according to a simplified Corey synthesis as described in DOS (German Unexamined Laid-Open Application) 2,328,131 with diisobutylaluminum hydride or lithium tri-tert.-butoxyaluminum hydride.

To introduce the hydroxy blocking groups, the 11,15-diol (PG numbering) is reacted with, for example, dihydropyran in methylene chloride or chloroform with the use of an acidic condensation agent, e.g. p-toluenesulfonic acid. The dihydropyran is used in an excess, preferably 4 to 10 times the theoretical quantity. The reaction is normally terminated after 15-30 minutes when conducted at 0° C.-30° C.

One possibility for producing the starting compounds acetylated in the 11-position is to react the lactol, etheri-

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fied in the 15-position (PG numbering), with acetic anhydride in pyridine. After liberating the lactolhydroxy group, a lactol of general Formula II is obtained.

The novel prostanoic acid derivatives of general Formula I are valuable pharmaceutical agents, since they show, with a similar spectrum of activity, a substantially stronger and, in particular, longer lasting effect than the corresponding natural prostaglandins.

The novel prostaglandin analogs of the E, D, and F type have a very strong luteolytic effect, i.e., for triggering luteolysis, at lower doses than the corresponding natural prostaglandins.

When recording the isotonic uterus contraction on narcotized rats and on the isolated rat uterus, it is found that the compounds of this invention are substantially more effective and their activities are of a longer duration than in case of the natural prostaglandins, as demonstrated by the following table, using compounds 1-8 of this invention as examples, in comparison to the natural PG $F_{2\alpha}$. The investigations were carried out on gravid rats according to the usual methods. Thus, gravid rats were treated, subcutaneously with the compounds of this invention. On the ninth day, the animals were sacrificed and the uteri examined for points of implantation.

TABLE

	Compound Investigated	Relative Effect PG $F_{2\alpha}$ = 1 on Abortion in Rats
1	Methyl ester of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18-19,20-pentanor-prostadienoic acid	300
2	Methyl ester of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,-15-trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic acid	30
3	(4-Phenyl)-phenacyl ester of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,-15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,-19,20-pentanor-prostadienoic acid	30
4	(4-Phenyl)-phenacyl ester of (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,-18,19,20-pentanor-prostadienoic acid	3
5	(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17-18,19,20-pentanor-prostadienoic acid	3
6	Methyl ester of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic acid	3
7	Methyl ester of (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic acid	10
8	Methyl ester of (5Z,13E)-8R,-9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2R }-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic acid	10

As demonstrated by the table, the compounds of this invention are of the same abortive effectiveness in doses which are 3 to 300 times lower per 1 mg. per animal than PG $F_{2\alpha}$.

The novel prostanoic acid derivatives are suitable, by one-time intrauterine application, for inducing menstruation or interrupting a pregnancy. They are furthermore suitable for snychronizing the sexual cycle in female mammals, such as cattle, monkeys, pigs, rabbits, etc.

The high dissociation of effectiveness of the compound according to the present invention manifests itself in their effect on other smooth-muscle organs, for example, on the guinea pig ileum or on the isolated rabbit trachea, where substantially lesser stimulation is observed than with natural prostaglandins.

Active agents of the PG E series according to the invention show in vitro, on the isolated rabbit trachea, a broncho-dilatory effect and greatly inhibit stomach acid secretion. The also have a regulating effect on cardiac dysrhythmias. The novel compounds of the PG A and PG E series additionally lower blood pressure and have a diuretic effect.

Active agents of the F series have a lower bronchoconstrictive effect than natural prostaglandin $F_{2\alpha}$, which is of great advantage for their therapeutic application.

For medical use, the active agents can be converted into a form suitable for inhalation or for oral or parenteral application.

For inhalation purposes, aerosol or spray solutions are advantageously prepared.

Suitable for oral application are, for example, tablets, dragees, or capsules.

For parenteral administration, sterile, aqueous or oily solutions which can be injected are utilized.

The invention also relates to medicinal agents comprise compounds of Formula I and customary auxiliary agents and carriers. Conventional excipients are pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic wetting agents, buffers, or salts for influencing osmotic pressure, etc. Sprayable aerosol preparations of compounds of Formula I, preferably in combination with a solid or liquid inert carrier material, are packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a freon.

The active agents of this invention are useful, in conjunction with the auxiliary substances known and customary in galenic pharmacy, in preparations for triggering abortion, for menstrual cycle control, or for the induction of labor. For the latter purpose, sterile, aqueous solutions can be employed containing 0.01-10 μg./ml. of the active ingredient and used in the form of an intravenous infusion solution. To produce aqueous, isotonic solutions, acids and salts of Formula I are espe-

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cially suitable. Alcohols, such as ethanol and propylene glycol, can be added to increase solubility.

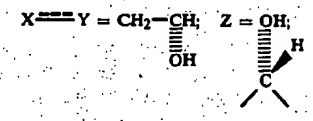
In addition to the compounds of the Examples hereinafter, illustrative embodiments of the compounds of Formula I are: Methylsulfamid of
(13E)-(8R,11R,12R,15R)-9-oxo-11,15-dihydroxy-15-({2RS}-1,3-benzodioxan-7-trifluoromethyl-2-yl)-16,17,18,19,20-pentanor-13-prostemoic acid
(4-phenyl)-phenacyl ester of (5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-({2RS}-1,3-benzodioxan-8-methoxy-2-yl)-16,17,18,19,20-pentanor-5-prostenoic acid
(4-bromo)-phenacyl ester of (5Z,13E)-(8R,11R,12R,15R)-9-oxo-11,15-dihydroxy-15-({2S}-1,3-benzodioxan-6-chloro-2-yl)-16,17,18,19,20-pentanor-5,13-prostadienoic acid
(4-phenyl)-phenacylester of (5Z,10Z,13E)-(8R,12S,15R)-9-oxo-15-hydroxy-15-({2R}-1,3-benzodioxan-6-bromo-2-yl)-16,17,18,19,20-pentanor-5,10,13-prostatrienoic acid
methylsulfamid of (8R,11R,12R,15R)-9-oxo-11,15-dihydroxy-15-({2RS}-1,3-benzodioxan-6,8-dichloro-2-yl)-16,17,18,19,20-pentanor-prostanoic acid

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLE 1

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OCH_3, OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

(a) Methyl Ester of 1,3-Benzodioxane-2-carboxylic Acid

Under ice water cooling, a solution of 12.4 g. of saligenin in 100 ml. of dimethylformamide was added dropwise to a suspension of 9.6 g. of 50% sodium hydride in 100 ml. of dimethylformamide. The reaction mixture was stirred overnight at room temperature.

Under ice cooling, 9 ml. of dichloroacetic acid was introduced into 50 ml. of dimethylformamide. A suspension of 5.3 g. of 50% strength sodium hydride in 150 ml. of dimethylformamide was added thereto under ice cooling. The sodium hydride can also be added without a solvent.

This sodium dichloroacetate solution was introduced dropwise at room temperature into the first-prepared saligenin disodium solution. The reaction mixture was agitated at 60° C. for a total of 5 hours, adding potassium iodide thereto. During the last three hours, the dimethylformamide was distilled off with an oil pump. The semisolid, brown residue was acidified with concentrated-aqueous citric acid solution to pH 3 and extracted with methylene chloride. The organic phase was dried over magnesium sulfate, concentrated on a forced circulation evaporator, and combined at about 10° C. with diazomethane solution. After 1 hour of agitation at room temperature, the excess diazomethane and the solvent were removed by means of a water-jet aspirator. The remaining substance was introduced into saturated sodium chloride solution, extracted with methylene chloride, and the organic phase was dried with magnesium sulfate, concentrated, and purified by column chromatography on silica gel with hexane/-5–10% ethyl acetate. Yield: 6 g. of the methyl ester of 1,3-benzodioxane-2-carboxylic acid; m.p. 28°–29° C.

(b) [2-Oxo-2-(1,3-benzodioxan-2-yl)-ethylidene]triphenylphosphorane

At room temperature under an argon atmosphere, 40 ml. of a 2.52-molar butyllithium solution in hexane was added dropwise to a suspension of 39 g. of triphenylmethylphosphonium bromide in 250 ml. of absolute ether; the reaction mixture was stirred for 15 hours, likewise under argon and at room temperature. A solution of 9.78 g. of the methyl ester of 1,3-benzodioxane-2-carboxylic acid in 100 ml. of absolute ether was added dropwise to the yellow gold solution, and the mixture was agitated for 1 hour at room temperature. The white precipitate was then filtered off, dissolved in water, and extracted with ether. The organic phase was combined with the filtrate, washed with water, dried over magnesium sulfate, and evporated to dryness. The residue was purified by column chromatography on silica gel with hexane/20–100% ethyl acetate and then recrystallized from ethyl acetate.

Yield: 12 g., m.p. 95°–98° C.

(c) (1S,5R,6R,7R)-6-[(E)-3-Oxo-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,-0]octan-3-one

Under an argon atmosphere, 7 g. of (1S,5R,6R,7R)-6-formyl-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one, E. J. Corey et al., J. Amer. Chem. Soc. 91, 5675 (1969), and 11.2 g. of [2-oxo-2-(1,3-benzodioxan-2-yl)-ethylidene]-triphenylphosphorane were agitated at room temperature for 16 hours in 300 ml. of benzene. The reaction mixture was then evaporated to dryness under vacuum. The residue was purified by column chromatography on silica gel with hexane/20–60% ethyl acetate as the eluent. Yield: 5 g. of an oil.

(d) (1S,5R,6R,7R,3'R)-6-[(E)-3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

A solution of 2 g. of the ketone obtained according to (c) in 140 ml. of absolute dimethoxyethane was combined with 140 ml. of ethereal zinc borohydride solution (preparation: "Neuere Methoden der praeparativen organischen Chemie" (More Recent Methods of Preparative Organic Chemistry), 4: 241, publishers: Verlag Chemie) and agitated under argon for 2 hours at room temperature. After dilution with 100 ml. of ether, the reaction solution was carefully combined with water, extracted with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness under vacuum. The reaction products were separated

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by column chromatography on silica gel with hexane/30–60% ethyl acetate as the eluent. The α-alcohol was eluted as the first product; yield: 0.8 g.

(e)

(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

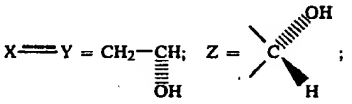
General Formula II: A=trans-CH=CH; R_2, R_3, R_4, R_5, R_6=hydrogen atoms; the OH-group on C-3' is in the α-position.

Under argon, 5.5 ml. of a 20% solution of diisobutylaluminum hydride in toluene was added to a solution, cooled to −60° C., of 550 mg. of the lactone alcohol produced in accordance with (d) in 20 ml. of absolute toluene; the mixture was stirred at −60° C. for 30 minutes, and the reaction was then terminated by the dropwise addition of 2 ml. of isopropanol. After adding 20 ml. of water, the mixture was stirred for 15 minutes at 0° C., then extracted with ethyl acetate and/or methylene chloride, shaken with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness under vacuum. Yield: 520 mg. of the crude product of the above lactol which was utilized without further purification for the next stage.

(f)

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

A solution of 3.46 g. of 4-carboxybutyltriphenylphosphonium bromide in 10 ml. of absolute dimethyl sulfoxide (DMSO) was combined with 14.98 ml. of a solution of methanesulfinylmethylsodium in absolute DMSO (preparation: 2 g. of 50% sodium hydride suspension was dissolved in 40 ml. of absolute DMSO at 70° C.); the mixture was agitated for 30 minutes at room temperature. This solution, a reddish-brown color, was added dropwise under water cooling to a solution of 520 mg. of the lactol obtained according to (e) in 5 ml. of absolute DMSO. The reaction mixture was then stirred for 2 hours under argon at 50° C., and thereafter most of the DMSO was removed by distillation on an oil pump (bath temperature 40°–50° C.). The residue was combined with 50 ml. of ice water and extracted three times with ether. This ether extract was discarded. The aqueous phase was acidified to pH 4 with 10% citric acid solution, and then extracted four times with an ether/-hexane mixture (1:1) and three times with methylene chloride. The organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to dryness. The residue was purified by chromatography on silica gel with methylene chloride/1–10% ethanol as the eluent. Yield: 310 mg.

(g) The prostaglandin acid obtained according to (f) was dissolved in methylene chloride and esterified with ethereal diazomethane solution. The residue of the evaporation was chromatographed on silica gel with methylene chloride/4% isopropanol as the eluent, thus obtaining the methyl ester of pro glandin-carboxylic acid set forth as Example 1.

Yield: 288 mg.

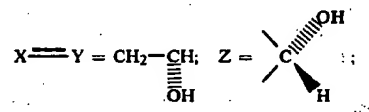
$[\alpha]_D^{23}$ = +0.8° (c=0.25; $CHCl_3$)

IR: 3400 (broad), 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 2

(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OCH_3, OH; R_2, R_3, R_4=hydrogen atoms; the OH-group on C-15 is in the β-position.

During the reaction of (1S,5R,6R,7R)-6-[(E)-3-oxo-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one, described in Example 1(d), the β-alcohol was eluted from the column as the second product:

(a)

(1S,5R,6R,7R,3'S)-6-[(E)-3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

Yield: 0.5 g.

(b)

(2RS,3aR,4R,5R,6aS,3'S)-4-[(E)-3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

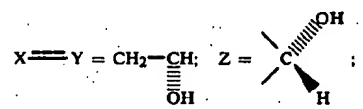
General Formula II: A=trans-CH=CH; R_2, R_3, R_4, R_5, R_6=H; the OH-group on C-3' is in the β-position.

410 mg. of the β-alcohol obtained in accordance with (a) was reacted analogously to the description of Example 1(e) with diisobutylaluminum hydride, thus obtaining 400 mg. of a crude product.

(c)

(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

The 400 mg. of lactol obtained in (b) was reacted without any further purification analogously to the procedure set forth in Example 1(f) with 2.66 g. of 4-carboxybutyltriphenylphosphonium bromide and 11.52 ml. of the methanesulfinylmethylsodium solution described in that example.

Yield: 220 mg.

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(d) The prostaglandin acid obtained in accordance with (c) was dissolved in methylene chloride and esterified with ethereal diazomethane solution. The residue of the evaporation was chromatographed on silica gel with methylene chloride/4% isopropanol as the eluent, thus obtaining the prostaglandincarboxylic acid methyl ester set forth as Example 2.

Yield: 198 mg.

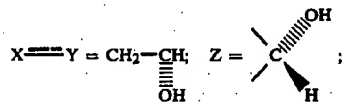
$[\alpha]_D^{23} = -0.8°$ (c=0.25; $CHCl_3$)

IR: 3400 (broad), 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 3

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OCH_3, OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

(a)

(1S,5R,6R,7R)-6-[(E)-3-Oxo-3-({2R}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

The compound was obtained in the form of colorless crystals by benzene/ether crystallization of the oil described in Example 1(c); m.p.: 129°–130° C.; $[\alpha]_D^{23} = -147.4°$ ($CHCl_3$).

(b)

(1S,5R,6R,7R,3'R)-6-[(E)-3-Hydroxy-3-({2R}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

According to Example 1(d), the α-alcohol was obtained from 1.5 g. of the ketone obtained according to Example 3(a) as the first product of the column chromatography by zinc borohydride reduction. Yield: 0.61 g.; $[\alpha]_D^{23} = -101.3°$ ($CHCl_3$).

(c)

(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-3-Hydroxy-3-({2R}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

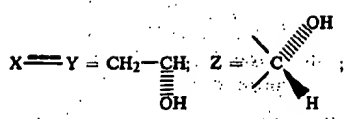
General Formula II: A=trans-CH=CH; R_2, R_3, R_4, R_5, R_6=hydrogen atoms; the OH-group on C-3' is in the α-position.

Analogously to the directions given in Example 1(e), 600 mg. of the α-alcohol obtained according to (b) is reacted with diisobutylaluminum hydride, thus obtaining 450 mg. of a crude product.

(d)

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OH; R_2, R_3, R_4=hydrogen atoms; the OH-group on C-15 is in the α-position.

The 450 mg. of lactol obtained in (c) were reacted without further purification analogously to the directions in Example 1(f) with 3.8 g. of 4-carboxybutyltriphenylphosphonium bromide and 16.5 ml. of the methanesulfinylmethylsodium solution described therein. Yield: 315 mg.

(e) The prostaglandin acid obtained in accordance with (d) was dissolved in methylene chloride and esterified with ethereal diazomethane solution. The residue of the evaporation was chromatographed on silica gel with methylene chloride/1–6% isopropanol as the eluent, thus obtaining the methyl ester of the prostaglandin-carboxylic acid set forth as Example 3. Yield: 299 mg.

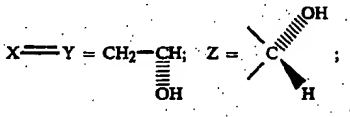
$[\alpha]_D^{23} = -21.2°$ (c=0.4; $CHCl_3$)

IR: 3400 (broad), 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 4

(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OCH_3, OH; R_2, R_3, R_4=hydrogen atoms; the OH-group on C-15 is in the β-position.

The β-alcohol was eluted from the column as the second product during the zinc borohydride reduction, disclosed under 3(b), of (1S,5R,6R,7R)-6-[(E)-3-oxo-3-({2R}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one (Example 3[a]):

(a)

(1S,5R,6R,7R,3'S)-6-[(E)-3-Hydroxy-3-({2R}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

Yield: 0.41 g.; $[\alpha]_D^{23} = -128°$ ($CHCl_3$).

(b)

(2RS,3aR,4R,5R,6aS,3'S)-4-[(E)-3-Hydroxy-3-({2R}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

General Formula II: A=trans-CH=CH; R_2, R_3, R_4, R_5, R_6=hydrogen atoms; the OH-group on C-3' is in the β-position.

Following the description of Example 1(e), 410 mg. of the β-alcohol obtained according to (a) was reacted with diisobutylaluminum hydride, thus obtaining 400 mg. of a crude product.

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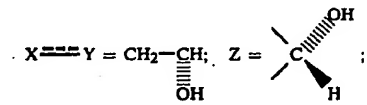
(c)

(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OH; R_2, R_3, R_4=hydrogen atoms; the OH-group on C-15 is in the β-position.

Analogously to the directions of Example 1(f), the 400 mg. of lactol obtained in (b) was reacted without any further purification with 2.66 g. of 4-carboxybutyltriphenylphosphonium bromide and 11.52 ml. of the methanesulfinylmethylsodium solution described therein. Yield: 230 mg.

(d) The prostaglandin acid obtained according to (c) was dissolved in methylene chloride and esterified with ethereal diazomethane solution. The residue of the evaporation was chromatographed on silica gel with methylene chloride/1-6% isopropanol as the eluent, thus obtaining the prostaglandin-carboxylic acid methyl ester indicated as Example 4.

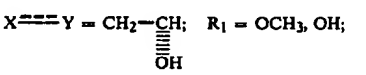
Yield: 212 mg. $[\alpha]_D^{23} = -46.4°$ (c=0.25; $CHCl_3$).

IR: 3400 (broad), 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 5

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

(a)

(1S,5R,6R,7R)-6-[(E)-3-Oxo-3-({2S}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

The mother liquor obtained according to Example 3(a) was chromatographed by column chromatography on silica gel with hexane/20-50% ethyl acetate as the eluent.

$[\alpha]_D^{23} = -18.8°$ ($CHCl_3$).

(b)

(1S,5R,6R,7R,3'R)-6-[(E)-3-Hydroxy-3-({2S}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

According to Example 1(d), 3 g. of the ketone obtained as described in Example 5(a) was used for producing, by zinc borohydride reduction, the α-alcohol as the first product isolated by repeated conducted column chromatography.

Yield: 1.1 g.

(c)

(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-3-Hydroxy-3-({2S}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

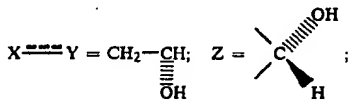
General Formula II: A=trans-CH=CH; R_2, R_3, R_4, R_5, R_6=H; the OH-group on C-3' is in the α-position.

Analogously to the disclosure in Example 1(e), 800 mg. of the α-alcohol obtained according to Example 5(b) was reacted with diisobutylaluminum hydride, thus producing 750 mg. of a crude product.

(d)

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

The 750 mg. of lactol obtained in (c) was reacted without further purification, analogously to the directions in Example 1(f), with 5.1 g. of 4-carboxybutyltriphenylphosphonium bromide and 22 ml. of the methanesulfinylmethylsodium solution described therein.

Yield: 480 mg.

(e) The prostaglandin acid obtained in accordance with (d) was dissolved in methylene chloride and esterified with ethereal diazomethane solution. The residue of the evaporation was chromatographed on silica gel with hexane/50-95% ethyl acetate as the eluent, thus obtaining the prostaglandin-carboxylic acid methyl ester indicated as Example 5.

Yield: 450 mg.

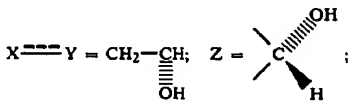
$[\alpha]_D^{23} = +51.2°$ (c=0.5; $CHCl_3$)

IR: 3400 (broad), 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 6

(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

During the zinc borohydride reduction, described in Example 5(b), of (1S,5R,6R,7R)-(6-[(E)-3-oxo-3-({2S}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]-octan-3-one (Example 5[a]), the β-alcohol was eluted as the second product from the column:

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(a)
(1S,5R,6R,7R,3'S)-6-[(E)-3-Hydroxy-3-({2S}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

Yield: 0.7 g.

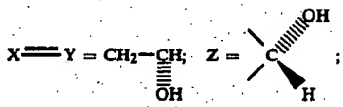
(b)
(2RS,3aR,4R,5R,6aS,3'S)-4-[(E)-3-Hydroxy-3-({2S}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

General Formula II: A=trans-CH=CH; R_2, R_3, R_4, R_5, R_6=H; the OH-group on C-3' is in the β-position.

600 mg. of the β-alcohol obtained according to Example 6(a) was reacted in accordance with Example 1(e) with diisobutylaluminum hydride, thus obtaining 470 mg. of a crude product.

(c)
(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



R_1=OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

The 470 mg. of lactol obtained in (b) was reacted without further purification analogously to the directions given in Example 1(f) with 3.8 g. of 4-carboxybutyltriphenylphosphonium bromide and 16.5 ml. of the methanesulfinylmethylsodium solution disclosed therein.

Yield: 330 mg.

(d) The prostaglandin acid obtained in accordance with (c) was converted analogously to Example 5(e) into the methyl ester of the prostaglandin-carboxylic acid.

Yield: 290 mg.

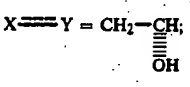
$[\alpha]_D^{23}=+50°$ (c=0.5; $CHCl_3$)

IR: 3400 (broad), 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 7

(5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

(a)
(1S,5R,6R,7R,3'R)-6-[(E)-3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-hydroxy-2-oxabicyclo[3,3,0]octan-3-one

A mixture of 1.97 g. of (1S,5R,6R,7R,3'R)-6-[(E)-3-hydroxy-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one (prepared in accordance with Example 1[d]) and 622 mg. of potassium carbonate (anhydrous) in 91 ml. of methanol (absolute) was agitated at room temperature for 2 hours under argon. The mixture was then poured into 90 ml. of 0.1 N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried with magnesium sulfate, and evaporated under vacuum. Chromatography of the crude product on silica gel (ether/ethyl acetate=7:3) yielded 1.20 g. of a colorless oil.

(b)
(1S,5R,6R,7R,3'R)-6-[(E)-3-({2RS}-1,3-Benzodioxan-2-yl)-1-propenyl]-3',7-bis(tetrahydropyranyloxy)-2-oxabicyclo[3,3,0]octan-3-one

At ice bath temperature, 6.1 ml. of freshly distilled dihydropyran and 15 mg. of p-toluenesulfonic acid were added to a solution of 1.85 g. of the diol obtained according to (a) in 50 ml. of methylene chloride; the mixture was stirred for 15 minutes at this temperature, diluted with methylene chloride, and shaken with sodium carbonate solution. The organic phase was washed with water, dried with magnesium sulfate, and evaporated under vacuum. After chromatography on silica gel (ether), 2.2 g. of the bis(tetrahydropyranyl)ether was obtained.

(c)
(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-3-({2RS}-1,3-Benzodioxan-2-yl)-1-propenyl]-3',5-bis(tetrahydropyranyloxy)perhydrocyclopenta[b]furan-2-ol

General Formula II: A=trans-CH=CH; R_2, R_3, R_4=H; R_5, R_6=THP; the OTHP-group on C-3' is in the α-position.

Under argon, 22 ml. of a 20% DIBAH solution in toluene was added dropwise to a solution of 2.2 g. of the lactone obtained according to (b) in 85 ml. of absolute toluene, cooled to −70° C. After thirty minutes, the reaction was terminated by the dropwise addition of isopropanol, and the mixture was stirred for 15 minutes at 0° C. while adding 30 ml. of water. Thereafter, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with magnesium sulfate, and evaporated under vacuum, thus obtaining 2.2 g. of lactol as a colorless oil.

(d)
(5Z,13E)-(8R,9S,11R,12R,15R)-9-Hydroxy-11,15-bis(-tetrahydropyranyloxy)-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

A solution of 9.5 g. of 4-carboxybutyltriphenylphosphonium bromide in 40 ml. of absolute dimethyl sulfoxide was combined with 34.7 ml. of a solution of methanesulfinylmethylsodium in absolute dimethyl sulfoxide which was added dropwise (solution: 2.5 g. of 50% sodium hydride suspension was agitated in 50 ml. of absolute dimethyl sulfoxide for 1 hour at 70° C.). The mixture was stirred for 30 minutes at room temperature. This ylid solution was subsequently added dropwise at 15° C. to a solution of 2.16 g. of the lactol obtained according to (c) in 40 ml. of absolute dimethyl sulfoxide within 15 minutes; the mixture was then stirred for 2 hours at 50° C. Thereafter, the solvent was removed by distillation under an oil pump vacuum and at 45° C.; the residue was taken up in 80 ml. of water and extracted three times with ether. The organic extract was discarded. The aqueous phase was acidified with 10%

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citric acid solution to pH 4–5 and extracted four times with a mixture of hexane/ether 1+1. The ether/hexane extract was washed with brine, dried with magnesium sulfate, and evaporated under vacuum. After chromatographing the residue of the evaporation on silica gel, 2.48 g. of the acid was eluted with ether as a colorless oil.

(e)

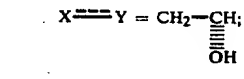
(5Z,13E)-(8R,11R,12R,15R)-9-Oxo-11,15-bis(tetrahydropyranyloxy)-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

A solution of 2.35 g. of the alcohol obtained according to (d) in 30 ml. of acetone was combined at −20° C. with 2.46 ml. of Jones reagent (J.Chem.Soc. 1953, 2555) and agitated for 30 minutes at −20° C. Thereafter, 3 ml. of isopropyl alcohol was added dropwise to the reaction mixture and the latter was stirred for 10 minutes at −20° C., then diluted with ether, and shaken three times with water. The organic phase was dried with magnesium sulfate and evaporated under vacuum, thus obtaining 2.1 g. of the ketone as a colorless oil.

(f)

(5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

2.1 g. of the bis(tetrahydropyranyl)ether obtained according to (e) was agitated for 5 hours at 40° C. in 42 ml. of a mixture consisting of 65 parts of glacial acetic acid, 35 parts of water, and 10 parts of tetrahydrofuran. Thereafter, the mixture was evaporated to dryness at 0.1 torr and the crude product was purified by column chromatography. With chloroform/ethanol 95+5, 450 mg. of the E_2 derivative was eluted as a colorless oil.

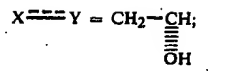
(g) At ice bath temperature, 7 ml. of an ethereal diazomethane solution was added dropwise to a solution of 130 mg. of the acid obtained according to (f) in 4 ml. of methylene chloride; the mixture was agitated for 2 minutes and then evaporated under vacuum. After chromatography of the crude product on silica gel (ether/dioxane 95:5), 56 mg. of the prostaglandin-carboxylic acid methyl ester set forth as Example 7 was obtained, in addition to mixed fractions, in the form of an oil which was completely uniform according to thin-layer chromatography.

IR: 3400 (broad), 1740, 1730, 1590, 1490, 980, 750 cm^{-1}

EXAMPLE 8

(5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

(a)

(1S,5R,6R,7R,3'S)-6-[(E)-3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-hydroxy-2-oxabicyclo[3,3,0]octan-3-one

2.16 g. of (1S,5R,6R,7R,3'S)-6-[(E)-3-hydroxy-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one (prepared according to Example 2[a]) and 687 mg. of anhydrous potassium carbonate was agitated for 2.5 hours in 99 ml. of methanol at room temperature. The reaction mixture was then combined with 99 ml. of 0.1 N HCl, agitated for 15 minutes, extracted with ethyl acetate, the organic phese was shaken with brine, dried, and evaporated under vacuum. The crude product was chromatographed on silica gel, thus obtaining 1.38 g. of the diol as a colorless oil.

(b)

(1S,5R,6R,7R,3'S)-6-[(E)-3-[{2RS}-1,3-Benzodioxan-2-yl)-1-propenyl]-3',7-bis(tetrahydropyranyloxy)-2-oxabicyclo[3,3,0]octan-3-one

At ice bath temperature, 4.5 ml. of dihydropyran (freshly distilled) and 10 mg. of p-toluenesulfonic acid were added to a solution of 1.38 g. of the diol obtained according to (a) in 30 ml. of methylene chloride; the mixture was stirred for 15 minutes at about 5° C., diluted with methylene chloride, shaken with sodium bicarbonate solution, washed with brine, dried with magnesium sulfate, and evaporated under vacuum. After chromatographing the crude product on silica gel (ether/hexane 8:2), 1.91 g. of the bis(tetrahydropyranyl)ether was obtained as a colorless oil.

(c)

(2RS,3aR,4R,5R,6aS,3'S)-4-[(E)-3-({2RS}-1,3-Benzodioxan-2-yl)-1-propenyl]-3',5-bis(tetrahydropyranyloxy)-perhydrocyclopenta[b]furan-2-ol

General Formula II: A=trans-CH↑CH; R_2, R_3, R_4=H; R_5, R_6=THP; the OTHP-group on C-3' is in the β-position.

Analogously to the directions in Example 7(c), 1.91 g. of the lactone produced according to (b) in 75 ml. of absolute toluene was reduced with 19 ml. of diisobutylaluminum hydride solution (DIBAH solution). After working up the reaction mixture as usual, 1.93 g. of lactol was obtained as a colorless oil.

(d)

(5Z,13E)-(8R,9S,11R,12R,15S)-9-Hydroxy-11,15-bis(-tetrahydropyranyloxy)-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

Analogously to the disclosure in Example 7(d), 1.93 g. of the lactol produced in accordance with (c) in 30 ml. of absolute DMSO was reacted with an ylene solution produced from 8.47 g. of 4-carboxybutyltriphenylphosphonium bromide and 31 ml. of methanesulfinylmethylsodium solution. After the usual work up, the crude product was purified by column chromatogra-

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phy. With ether, 2.1 g. of the acid was eluted as a colorless oil.

(e)

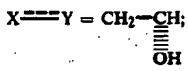
(5Z,13E)-(8R,11R,12R,15S)-9-Oxo-11,15-bis(tetrahydropyranyloxy)-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

In analogy to the directions given in Example 7(e), 2.05 g. of the alcohol obtained according to (d) in 50 ml. of acetone was oxidized with 2.14 ml. of Jones reagent at −20° C. The mixture was worked up, thus producing 1.84 g. of the ketone as a colorless oil.

(f)

(5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-1,6,17,18,19,20-pentanorprostadienoic Acid

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

Analogously to the directions in Example 7(f), 1.84 g. of the bis(tetrahydropyranyl)ether obtained according to (e) was agitated with 18 ml. of the acetic acid/THF mixture. After working up the reaction mixture and chromatographing same on silica gel (chloroform/ethanol=95:5), 528 mg. of the E_2 derivative was obtained as a colorless oil.

(g) 98 mg. of the prostaglandin acid obtained according to (f) was converted into the prostaglandin-carboxylic acid methyl ester analogously to Example 7(g).

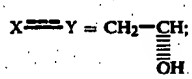
Yield: 76 mg.

IR: 3400 (broad), 1740, 1730, 1590, 1490, 980, 750 cm^{-1}

EXAMPLE 9

(5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

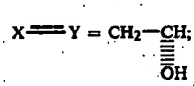
These compounds are prepared analogously to Example 7(a)–(g) from the starting compound produced according to Example 3(b) Yield: 400 mg. of prostadienoic acid as a colorless oil; 60 mg. of the methyl ester of the prostadienoic acid (produced from 130 mg. of the acid).

IR: 3500-3400, 1740, 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 10

(5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OCH_3, OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

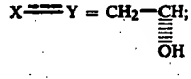
These compounds are prepared in analogy to Examples 8(a) (g) from the starting compound produced according to Example 4(a). Yield: 510 mg. of prostadienoic acid as a colorless oil; 70 mg. of the prostadienoic acid methyl ester (from 100 mg. of the acid).

IR: 3500–3400, 1740, 1730, 1590, 1490, 980, 750 cm^{-1}.

EXAMPLE 11

(5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OCH_3, OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

These compounds are produced analogously to Examples 7(a)–(g) from the starting compound prepared according to Example 5(b).

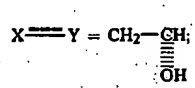
Yield: 310 mg. of prostadienoic acid as a colorless oil; 50 mg. of the prostadienoic acid methyl ester (from 120 mg. of the acid).

IR: 3500–3400, 1740, 1730, 1590, 1490, 980, 750 cm^{-1}

EXAMPLE 12

5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans-CH=CH; B=cis-CH=CH;



Z=C=O; R_1=OCH_3, OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

These compounds are prepared in analogy to Examples 8(a)–(g) from the starting compound produced according to Example 6(a).

Yield: 410 mg. of prostadienoic acid; 150 mg. of the prostadienoic acid methyl ester (from 210 mg. of the acid).

IR: 3500–3400, 1740, 1730, 1590, 1490, 980, 750 cm^{-1}.

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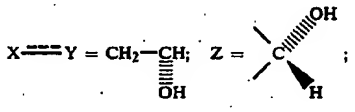
EXAMPLE 13

(5Z)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Esther Thereof

General Formula I: A=CH_2—CH_2; B=cis-CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

(a)

(1S,5R,6R,7R,3'R)-6-[3-Hydroxy-3-({2S}-1,3-benzodioxan-2-yl)-1-propyl]-7-benzoyloxy-2-oxabicyclo[3,3,-0]octan-3-one

Under a hydrogen atmosphere, 2.3 g. of the α-alcohol obtained according to Example 1(d) and 230 mg. of palladium on charcoal (10%) was shaken for 2 hours in 40 ml. of ethyl acetate. After filtration and evaporation, 2.3 g. of the above alcohol was obtained as a colorless oil.

IR: 3600, 1775, 1720, 1590, 1490, 770 cm^{-1}.

No olefinic protons could be detected in the NMR spectrum.

(b)

(1S,5R,6R,7R,3'R)-6-[3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propyl]-7-hydroxy-2-oxabicyclo[3,3,-0]octan-3-one

By treatment according to Example 7(a), 1.34 g. of the saturated diol was obtained in the form of a colorless oil from 2.20 g. of the saturated alcohol obtained in accordance with (a).

IR: 3600 (strong), 1775, 1590, 1490, 760 cm^{-1}.

(c)

1S,5R,6R,7R,3'R)-6-[3-({2RS}-1,3-Benzodioxan-2-yl)-1-propyl]-3',7-bis(tetrahydropyranyloxy)-2-oxabicyclo[3,3,0]octan-3-one

From 1.13 g. of the diol obtained according to (b), 1.08 g. of the above bis(tetrahydropyranyl)ether was obtained as a colorless oil from dihydropyran analogously to Example 7(b)

IR: 1775, 1590, 1490, 1100, 760 cm^{-1}.

(d)

(2RS,3aR,4R,5R,6aS,3'R)-4-[3-({2RS}-1,3-Benzodioxan-2-yl)-1-propyl]-3,5-bis(tetrahydropyranyloxy)perhydrocyclopenta[b]furan-2-ol

General Formula II: A=CH_2—CH_2; R_2, R_3, R_4=H; R_5, R_6=THP; the OTHP-group on C-3' is in the α-position.

According to Example 7(c), 1.06 g. of the above lactol was produced as a colorless oil by the reduction of 1.08 g. of the bis(tetrahydropyranyl)ether prepared according to (c).

IR* 3600, 1590, 1490, 1100, 760 cm^{-1}.

(e)

(5Z)-(8R,9S,11R,12R,15R)-9-Hydroxy-11,15-bis-(tetrahydropyranyloxy)-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

1.06 g. of the lactol obtained according to (d) was converted according to Example 7(d) into 866 mg. of the above prostenoic acid.

IR: 3600–3400, 1710, 1590, 1490, 1100, 760 cm^{-1}.

(f)

(5Z)-(8R,9S,11R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

310 mg. of the compound produced in accordance with (e) was agitated in 9 ml. of a mixture of acetic acid/water/tetrahydrofuran=65:35:10 for 3 hours at 50° C. The mixture was then evaporated to dryness under vacuum. Chromatograpy on 10 g. of silica gel (chloroform/ethanol 4+1) yielded 211 mg. of the above compound as a colorless oil.

IR: 3600–3300, 1710, 1590, 1490, 760 cm^{-1}.

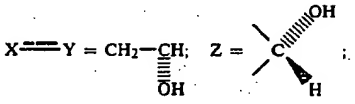
(g) At ice bath temperature, 7 ml. of an ethereal diazomethane solution was added dropwise to a solution of 130 mg. of the acid obtained according to (f) in 4 ml. of methylene chloride; the mixture was agitated for 15 minutes and then evaporated under vacuum. After chromatography of the crude product on silica gel (methylene chloride/3% isopropanol), 90 mg. of the prostaglandin-carboxylic acid methyl ester set forth as Example 13 was obtained.

IR: 3600–3300, 1730, 1590, 1490, 760 cm^{-1}.

EXAMPLE 14

(5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=CH_2—CH_2; B=cis-CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

(a)

(1S,5R,6R,7R,3'S)-6-[3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

Analogously to Example 13(a), 2.4 g. of the β-alcohol obtained according to Example 2(a) was hydrogenated to 2.4 g. of the above-mentioned saturated alcohol, obtained in the form of a colorless oil.

IR: 3600, 1775, 1720, 1590, 1490, 770 cm^{-1}.

(b)

(1S,5R,6R,7R,3'S)-6-[3-Hydroxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propyl]-7-hydroxy-2-oxabicyclo[3,3,-0]octan-3-one

By treatment with potassium carbonate according to Example 7(a), 1.39 g. of the saturated diol was produced as a colorless oil from 2.3 g. of the saturated alcohol obtained according to (a).

IR: 3600 (strong), 1775, 1590, 1490, 760 cm^{-1}.

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(c)

(1S,5R,6R,7R,3'S)-6-[3-({2RS}-1,3-Benzodioxan-2-yl)-1-propyl]-3',7-bis(tetrahydropyranyloxy)-2-oxabicyclo[3,3,0]octan-3-one

From 1.0 g. of the diol obtained according to (b), 0.93 g. of the above bis(tetrahydropyranyl)ether was produced as a colorless oil with dihydropyran analogously to Example 7(b).

IR: 1775, 1590, 1490, 1100, 760 cm^{-1}.

(d)

(2RS,3aR,4R,5R,6aS,3'S)-4-[3-({2RS}-1,3-Benzodioxan-2-yl)-1-propyl]-3',5-bis(tetrahydropyranyloxy)perhydrocyclopenta[b]furan-2-ol

According to Example 7(c), reduction of 0.74 g. of the bis(tetrahydropyranyl)ether produced according to (c) yielded 0.7 g. of the above lactol as a colorless oil.

IR: 3600, 1590, 1490, 1100, 760 cm^{-1}.

(e)

(5Z)-(8R,9S,11R,12R,15S)-9-Hydroxy-11,15-bis(tetrahydropyranyloxy)-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

According to Example 7(d), 0.7 g. of the lactol obtained as described in (d) was converted into 0.51 g. of the above prostenoic acid.

IR: 3600–3400, 1710, 1590, 1490, 1100, 760 cm^{-1}.

(f)

(5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

Analogously to the directions given in Example 13(f), 219 mg. of the above compound was obtained as a colorless oil from 345 mg. of the triol obtained according to (e).

IR: 3600–3300, 1710, 1590, 1490, 760 cm^{-1}.

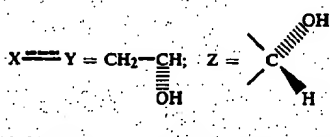
(g) Analogously to the esterification step described in Example 13(g), 120 mg. of the acid produced according to (f) yielded 85 mg. of the prostaglandin-carboxylic acid methyl ester set forth as Example 14.

IR: 3600–3300, 1730, 1590, 1490, 755 cm^{-1}.

EXAMPLE 15

(5Z)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=CH_2—CH_2; B=cis—CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

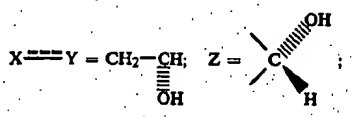
Starting with the α-alcohol obtained according to Example 3(b), the title compounds were obtained analogously to the reaction stages described for Examples 13(a)–(g).

IR (Methyl ester): 3500–3300, 1730, 1590, 1490, 760 cm^{-1}.

EXAMPLE 16

(5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=CH_2—CH_2; B=cis—CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

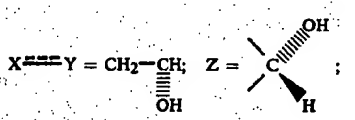
Starting with the β-alcohol obtained according to Example 4(a), the title compounds were produced analogously to the reaction stages described for Examples 14(a)–(g).

IR (Methyl ester): 3400 (broad), 1730, 1590, 1490, 760 cm^{-1}.

EXAMPLE 17

(5Z)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=CH_2—CH_2; B=cis—CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

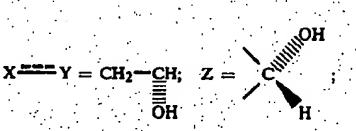
Starting with the α-alcohol obtained according to Example 5(b), the title compounds were obtained analogously to the reaction stages described for Example 13(a)–(g).

IR (Methyl ester): 3400 (broad), 1735, 1590, 1490, 760 cm^{-1}.

EXAMPLE 18

(5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=CH_2—CH_2; B=cis—CH=CH;



R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

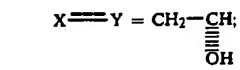
Starting with the β-alcohol produced according to Example 6(a), the title compounds were obtained analogously to the reaction stages described in Examples 14(a)–(g).

IR (Methyl ester): 3400 (broad), 1735, 1590, 1490, 760 cm^{-1}.

EXAMPLE 19

(5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: $A=CH_2—CH_2$; B=cis—CH=CH;



Z=>C=O; $R_1=OCH_3$,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

(a)

(5Z)-(8R,11R,12R,15R)-11,15-Bis(tetrahydropyranyloxy)-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

Analogously to Example 7(e), 300 mg. of the compound obtained according to Example 13(e) was converted by oxidation into the above-mentioned compound, thus obtaining 210 mg. of the product as a colorless oil.

IR: 3600–3300, 1740, 1710, 1590, 1490, 760 cm^{-1}.

(b)

(5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

In accordance with Example 7(f), 150 mg. of the compound obtained according to (a) yielded 90 mg. of the above compound as a colorless oil.

IR: 3600–3400, 1740, 1710, 1590, 1490, 760 cm^{-1}.

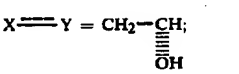
(c) Analogously to Example 7(g), 90 mg. of the acid obtained according to (b) yielded 75 mg. of the prostaglandincarboxylic acid methyl ester.

IR: 3600–3400, 1740, 1730, 1590, 1490, 750 cm^{-1}.

EXAMPLE 20

(5Z)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: $A=CH_2—CH_2$; B=cis—CH=CH;



Z=>C=O; $R_1=OCH_3$,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

(a)

(5Z)-(8R,11R,12R,15S)-11,15-Bis(tetrahydropyranyloxy)-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

By oxidation analogously to Example 7(e), 280 mg. of the compound obtained according to Example 14(e) was converted into the above compound, yielding 180 mg. as a colorless oil.

IR: 3600–3300, 1740, 1710, 1590, 1490, 760 cm^{-1}.

(b)

(5Z)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid

According to Example 7(f), 145 mg. of the compound produced according to (a) was converted to 80 mg. of the above diol.

IR: 3600–3400, 1740, 1710, 1590, 1490, 755 cm^{-1}.

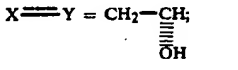
(c) Analogously to Example 7(g), 80 mg. of the acid produced according to (b) yielded 56 mg. of the above-mentioned prostaglandin-carboxylic acid methyl ester.

IR: 3600–3400, 1740, 1730, 1590, 1490, 755 cm^{-1}.

EXAMPLE 21

(5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: $A=CH_2—CH_2$; B=cis—CH=CH;



Z=>C=O; $R_1=OCH_3$,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

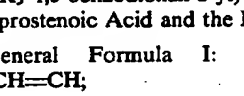
Starting with the derivative of Example 15 corresponding to Example 13(e), the title compounds were obtained analogously to the reaction stages described for Examples 19(a)–(c).

IR (Methyl ester): 3500–3400, 1740, 1730, 1590, 1490, 750 cm^{-1}.

EXAMPLE 22

(5Z)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: $A=CH_2—CH_2$; B=cis—CH=CH;



Z=>C=O; $R_1=OCH_3$,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

Starting with the derivative of Example 16 corresponding to Example 14(e), the title compounds were obtained analogously to the reaction stages described for Examples 19(a)–(c).

IR (Methyl ester): 3600–3400, 1740, 1730, 1590, 1490, 755 cm^{-1}.

EXAMPLE 23

(5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: $A=CH_2—CH_2$; B=cis—CH=CH;

Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

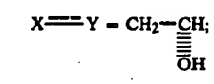
Starting with the derivative of Example 17 corresponding to Example 13(e), the title compounds were produced in analogy to the reaction stages described for Examples 19(a)-(c).

IR (Methyl ester): 3600-3400, 1740, 1730, 1590, 1490, 755 cm^{-1}.

EXAMPLE 24

(5Z)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=CH_2—CH_2; B=cis—CH=CH;



Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

Starting with the derivative of Example 18 corresponding to Example 14(e), the title compounds were produced in analogy to the reaction stages described for Example 19(a)-(c).

IR (Methyl ester): 3500-3400, 1740, 1730, 1590, 1490, 750 cm^{-1}.

EXAMPLE 25

(5Z,10Z,13E)-(8R,12S,15R)-15-Hydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH; X=====Y=CH=CH; Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

A solution of 88 mg. of (5Z,13E)-(8R,11R,12R,15R)-11,15-dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid (from Example 7[f]) in 6 ml. of 90% acetic acid was stirred for 19 hours at 60° C. and then evaporated under vacuum. Chromatography on silica gel (ether/3% dioxane) and subsequent etherification of the prostatrienoic acid with ethereal diazomethane solution yielded 45 mg. of the title compound as an oil having a slightly yellow coloring.

IR (Methyl ester): 3600-3300, 1730, 1700, 1590, 1490, 980, 760 cm^{-1}.

EXAMPLE 26

(5Z,10Z,13E)-(8R,12S,15S)-15-Hydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH; X=====Y=CH=CH; Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

According to the directions given in Example 25, the title compounds were prepared from the compound described in Example 8(f).

IR (Methyl ester): 3500-3300, 1730, 1705, 1590, 1490, 980, 760 cm^{-1}.

EXAMPLE 27

(5Z,10Z,13E)-(8R,12S,15R)-15-Hydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH; X=====Y=CH=CH; Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

According to the directions given in Example 25, the title compounds were obtained from the compound disclosed in Example 9(f).

IR (Methyl ester): 3600-3300, 1730, 1700, 1585, 1490, 980, 760 cm^{-1}.

EXAMPLE 28

(5Z,10Z,13E)-(8R,12S,15S)-15-Hydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH; X=====Y=CH=CH; Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

According to the disclosure of Example 25, the title compounds were produced from the compound described in Example 10(f).

IR (Methyl ester): 3600-3300, 1730, 1700, 1590, 1490, 980, 760 cm^{-1}.

EXAMPLE 29

(5Z,10Z,13E)-(8R,12S,15R)-15-Hydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH; X=====Y=CH=CH; Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

According to the directions set forth in Example 25, the title compounds were produced from the compound described in Example 11(f).

IR(Methyl ester): 3500-3300, 1730, 1700, 1590, 1485, 980, 760 cm^{-1}.

EXAMPLE 30

(5Z,10Z,13E)-(8R,12S,15S)-15-Hydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH; X=====Y=CH=CH; Z=>C=O; R_1=OCH_3,OH; R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

According to the directions given in Example 25, the title compounds were produced from the compound disclosed in Example 12(f).

IR (Metyhl ester): 3600-3300, 1730, 1700, 1590, 1490, 980, 760 cm^{-1}.

EXAMPLE 31

(13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=CH_2—CH_2;

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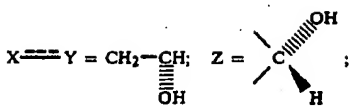


$R_1 = OCH_3, OH$; R_2, R_3, $R_4 = H$; the OH-group on C-15 is in the α-position.

150 mg. of the compound obtained according to Example 1(f) and Example 1(g), respectively, was mixed with 15 mg. of 10% palladium on charcoal and stirred with 15 ml. of ethyl acetate for 2 hours at −20° C. under a hydrogen atmosphere. After filtration, the reaction mixture was evaporated to dryness under vacuum, thus obtaining 140 mg. of the title compound as a colorless oil.

IR (Methyl ester): 3600–3300, 1730, 1590, 1490, 980, 760 cm^{-1}.

The NMR spectrum showed only two olefinic protons.

EXAMPLE 32

Analogously to Example 31, the following compounds can be produced from the corresponding starting compounds 2(d), 3(e), 4(d), 5(e), 6(d):

(13E)-(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,9S,11R,15R)-9,11,15-trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,9S,11R,15S)-9,11,15-trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,9S,11R,15R)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,9S,11R,15S)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof.

EXAMPLE 33

By interposing in the reaction sequence leading to the compounds of Examples 7–12 a reduction of compounds 7(d), 8(d), 9(d), 10(d), 11(d), 12(d) analogously to the process described for Example 31, then the following compounds are obtained:

(13E)-(8R,11R,12R,15R)-11,15-dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,11R,12R,15S)-11,15-dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,11R,12R,15R)-11,15-dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,11R,12R,15S)-11,15-dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

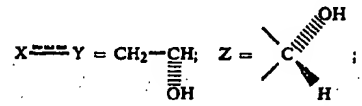
(13E)-(8R,11R,12R,15R)-11,15-dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof;

(13E)-(8R,11R,12R,15S)-11,15-dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid and the methyl ester thereof.

EXAMPLE 34

(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic Acid and the Methyl Ester Thereof

General Formula I: A=B=CH_2—CH_2;



$R_1 = OCH_3, OH$; R_2, R_3, $R_4 = H$; the OH-group on the C-15 is in the α-position.

At room temperature and under a hydrogen atmosphere, 432 mg. of the ester or acid obtained according to Example 1, 45 mg. of palladium on charcoal (10%), and 10 ml. of ethyl acetate were shaken until 2 millimoles of hydrogen had been absorbed. Filtration and evaporation resulted in 420 mg. of the above compound as a colorless oil.

IR (Methyl ester): 3600-3400, 1730, 1590, 1490, 760 cm^{-1}.

EXAMPLE 35

Analogously to the process described in Example 34, the following derivatives were obtained with the compounds of Examples 2–6:

(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid and the methyl ester thereof;

(8R,9S,11R,12R,15R)-9,11,15-trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid and the methyl ester thereof;

(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid and the methyl ester thereof;

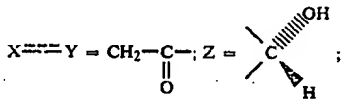
(8R,9S,11R,12R,15R)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid and the methyl ester thereof;

(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid and the methyl ester thereof.

EXAMPLE 36

(5Z,13E)-(8R,9S,12R,15R)-9,15-Dihydroxy-11-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH;



$R_1 = OCH_3, OH$; R_2, R_3, $R_4 = H$; the OH-group on C-15 is in the α-position.

(a)

(1S,5R,6R,7R,3'R)-6-[(E)-3-Tetrahydropyranyloxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-benzoyloxy-2-oxabicyclo[3,3,0]octan-3-one

At ice bath temperature, 3 ml. of freshly distilled dihydropyran and 10 mg. of p-toluenesulfonic acid were added to a solution of 2.4 g. of the α-alcohol ob-

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tained according to Example 1(d) in 50 ml. of methylene chloride; the mixture was agitated for 15 minutes at this temperature, diluted with methylene chloride, and shaken with sodium bicarbonate solution. The organic phase was washed with water, dried with magnesium sulfate, and evaporated under vacuum. Yield: 2.8 g. of the product.

(b)

(1S,5R,6R,7R,3'R)-6-[(E)-3-Tetrahydropyranyloxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-7-hydroxy-2-oxabicyclo[3,3,0]octan-3-one

A mixture of the 2.8 g. of product obtained according to (a) and 765 mg. of potassium carbonate (anhydrous) in 110 ml. of methanol (absolute) was stirred for 2 hours at room temperature under argon. The mixture was then diluted with ethyl acetate and washed with saturated sodium chloride solution so that the mixture became neutral. The organic phase was dried over magnesium sulfate and evaporated under vacuum, thus obtaining 1.85 g. of the title compound.

(c)

(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-3-Tetrahydropyranyloxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-5-hydroxyperhydrocyclopenta[b]furan-2-ol

Under argon, 22 ml. of a 20% DIBAH solution in toluene was added dropwise to a solution, cooled to −70° C., of 1.85 g. of the lactone obtained according to (b) in 90 ml. of absolute toluene. After 30 minutes, the reaction was terminated by the dropwise addition of isopropanol and agitated while adding 30 ml. of water for 15 minutes at 0° C. Thereafter, the mixture was extracted with ethyl acetate, washed with brine, dried with magnesium sulfate, and evaporated under vacuum. Yield: 1.8 g. of the title compound as a colorless oil.

(d)

(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-3-Tetrahydropyranyloxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-2,5-diacetoxyperhydrocyclopenta[b]-furan-2-ol

1.8 g. of the lactol obtained according to (c) was agitated at room temperature in a mixture of 10 ml. of acetic anhydride and 25 ml. of pyridine for 8 hours. After the solvent had been removed under vacuum, 2.0 g. of the title compound was produced.

(e)

(2RS,3aR,4R,5R,6aS,3'R)-4-[(E)-3-Tetrahydropyranyloxy-3-({2RS}-1,3-benzodioxan-2-yl)-1-propenyl]-5-acetoxyperhydrocyclopenta[b]furan-2-ol

2.0 g. of the diacetate obtained according to (d) was maintained for 15 minutes at 25° C. in a mixture of 5 parts of glacial acetic acid, 5 parts of water, and one part of tetrahydrofuran. The mixture was then stirred into a sodium bicarbonate solution and washed neutral. The organic phase was concentrated, and the residue was purified by column chromatography on silica gel with ether/pentane=1:1. Yield: 1.5 g. of the title compound.

(f)

(5Z,13E)-(8R,9S,11R,12R,15R)-9-Hydroxy-11-acetoxy-15-tetrahydropyranyloxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

26.3 ml. of a solution of methanesulfinylmethylsodium in absolute DMSO (solution: 2.5 g. of 50% sodium hydride suspension was stirred in 50 ml. of DMSO for 1 hour at 70° C.) was added dropwise to a solution of 7.2 g. of 4-carboxybutyltriphenylphosphonium bromide in 30 ml. of absolute dimethyl sulfoxide, and the mixture was stirred for 30 minutes at room temperature. This ylid solution was then added dropwise within 15 minutes to a solution of 1.5 g. of the lactol obtained according to (e) in 30 ml. of absolute DMSO; then, the mixture was agitated for 2 hours at 50° C. The solvent was thereafter extensively removed by distillation under an oil pump vacuum and at 45° C. The residue was taken up in 70 ml. of water and extracted three times with ether. The organic extract was discarded. The aqueous phase was acidified with 10% citric acid solution to pH 4–5 and extracted four times with a mixture of hexane/ether=1:1. The ether/hexane extract was washed with brine, dried over magnesium sulfate, and evaporated under vacuum. After chromatography of the residue on silica gel, 1.1 g. of the title compound was eluted as a colorless oil with ether.

(g)

(5Z,13E)-(8R,9S,11R,12R,15R)-9,15-Bis(tetrahydropyranyloxy)-11-acetoxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

A methylene chloride solution of 1.1 g. of the compound obtained according to (f) was combined at ice bath temperature with 2.2 ml. of dihydropyran and 6 mg. of p-toluenesulfonic acid and agitated for 15 minutes at this temperature. Subsequently the mixture was diluted with methylene chloride, extracted with sodium bicarbonate solution, the organic phase washed with water, dried over magnesium sulfate, and concentrated. The residue was treated for 15 minutes at 25° C. with a glacial acetic acid/water/THF mixture (5/5/1) and then introduced under agitation into a sodium bicarbonate solution and washed neutral. After the organic phase had been concentrated, 1.2 g. of a colorless oil was obtained as the product.

(h)

(5Z,13E)-(8R,9S,11R,12R,15R)-9,15-Bis(tetrahydropyranyloxy)-11-hydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

The 1.2 g. of product obtained according to (g) was reacted analogously to the directions given in (b) with potassium carbonate and methanol, thus obtaining 0.8 g. of the title compound.

(i)

(5Z,13E)-(8R,9S,12R,15R)-9,15-Bis(tetrahydropyranyloxy)-11-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

A solution of 0.8 g. of the alcohol obtained according to (h) in 10 ml. of acetone was mixed at −20° C. with 0.84 ml. of Jones reagent and then agitated for 30 minutes at −20° C. Thereafter, 1 ml. of isopropanol was added dropwise to the reaction mixture and the latter was stirred for 10 minutes at −20° C., then diluted with ether, and extracted three times with water. The organic phase was dried over magnesium sulfate and evaporated under vacuum, thus producing 725 mg. of the ketone as a colorless oil.

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(j)
(5Z,13E)-(8R,9S,12R,15R)-9,15-Dihydroxy-11-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid

650 mg. of the bis(tetrahydropyranyl)ether produced according to (i) was agitated for 6 hours at 50° C. in 15 ml. of a mixture consisting of 65 parts of glacial acetic acid, 35 parts of water, and 10 parts of tetrahydrofuran. Thereafter, the mixture was evaporated to dryness at 0.1 torr, and the crude product was purified by column chromatography. With methylene chloride/5–8% ethanol 280 mg. of the title compound was eluted.

(k) At ice bath temperature, 7 ml. of an ethereal diazomethane solution was added dropwise to a solution of 140 mg. of the acid obtained according to (j) in 10 ml. of methylene chloride. The mixture was agitated for 10 minutes and then evaporated under vacuum. Chromatography of the crude product on silica gel with ether/-dioxane=95/5 as the eluent yielded 80 mg. of the prostaglandin-carboxylic acid methyl ester of the D-type indicated as Example 36.

IR: 3500–3300, 1740, 1730, 1590, 1485, 980, 760 cm^{-1}.

EXAMPLE 37

Analogously to the process described in Example 36, the following derivatives were produced, starting with the compounds of Examples 2(a), 3(b), 4(a), 5(b), and 6(a):

(5Z,13E)-(8R,9S,12R,15S)-9,15-dihydroxy-11-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid and the methyl ester thereof;

(5Z,13E)-(8R,9S,12R,15R)-9,15-dihydroxy-11-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid and the methyl ester thereof;

(5Z,13E)-(8R,9S,12R,15S)-9,15-dihydroxy-11-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid and the methyl ester thereof;

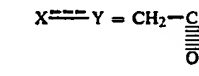
(5Z,13E)-(8R,9S,12R,15R)-9,15-dihydroxy-11-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid and the methyl ester thereof;

(5Z,13E)-(8R,9S,12R,15S)-9,15-dihydroxy-11-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid and the methyl ester thereof.

EXAMPLE 38

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxane-6-brom-2-yl)-16,17,18,19,20-pentanorprostadienoic Acid and the Methyl Ester Thereof

General Formula I: A=trans—CH=CH; B=cis—CH=CH;



R_1=OCH_3,OH: R_2, R_4=H; R_3=Br (in the p-position with respect to the phenolic oxygen); the OH-group on C-15 is in the α-position.

(a) 5-Bromo-2-hydroxybenzyl Alcohol

At 0°–5° C., 11.5 ml. of bromine in 100 ml. of carbon tetrachloride was added dropwise to a suspension of 24.8 g. of saligenin and 24 g. of calcium carbonate in a solvent mixture of 200 ml. of carbon tetrachloride and 220 ml. of methylene chloride. The reaction mixture was stirred for 24 hours at room temperature, then filtered, and the precipitate was washed with carbon tetrachloride. The CCl_4/CH_2Cl_2 phase was discarded. The solid substance was taken up in ethyl acetate/water, and the organic phase was separated, dried over magnesium sulfate, and evaporated to dryness. The residue was recrystallized from methylene chloride, thus obtaining colorless crystal flakes (24 g.). Melting point: 107°–109° C. (methylene chloride).

(b) 1,3-Benzodioxane-6-bromo-2-carboxylic Acid Methyl Ester

Under ice water cooling, a solution of 20.3 g. of the 5-bromo-2-hydroxybenzyl alcohol obtained according to (a) in 110 ml. of dimethylformamide was added dropwise to a suspension of 9.6 g. of 50% sodium hydride in 100 ml. of dimethylformamide. The reaction mixture was stirred overnight at room temperature. Thereafter, 8.62 ml. of dichloroacetic acid was added dropwise under ice cooling in 100 ml. of dimethylformamide. Under further ice cooling, 5.04 g. of 50% sodium hydride was then added to the reaction mixture in incremental portions. This sodium dichloroacetate solution was agitated for 30 minutes at room temperature and then introduced dropwise into the first-prepared bromosaligenin disodium solution. After the addition of 1.5 g. of sodium iodide, the reaction mixture was agitated for 4.5 hours at 60° C.; during the last 2.5 hours, the largest part of the dimethylformamide was distilled off under vacuum during this procedure. After cooling, the residue was acidified to pH 3 with aqueous citric acid solution, then saturated with sodium chloride, and extracted repeatedly with methylene chloride. The organic phase was dried over magnesium sulfate, concentrated with the aid of a forced-circulation evaporator, and combined at 0° C. with ethereal diazomethane solution until there was no longer any evolution of gas, and the reaction solution assumed permanently a yellow coloring. The solvent was removed after stirring for one-half hour at room temperature under vacuum, together with excess diazomethane. The remaining, light-colored crystalline slurry was purified by column chromatography on silica gel with methylene chloride or hexane/10% ethyl acetate as the eluent.

Yield: 12.6 g., m.p. 120° C. (matted, small needles of methylene chloride/hexane).

(c)
[2-Oxo-2-(1,3-benzodioxane-6-brom-2-yl)-ethylidene]-triphenylphosphorane

Under ice cooling and under an argon atmosphere, 15.63 ml. of a 2.15-molar butyllithium solution in hexane was added dropwise to a suspension of 13 g. of triphenylmethylphosphonium bromide (4 hours of drying at 40° C. with the use of an oil pump) in 85 ml. of absolute ether. The mixture was then agitated for 15 hours at room temperature. The yellow ylene solution was combined dropwise with 4.59 g. of the 1,3-benzodioxane-6-bromo-2-carboxylic acid methyl ester obtained according to (b) in 75 ml. of absolute benzene, and the mixture was stirred for 1 hour at room temperature. The white precipitate was filtered off, dissolved in water, and extracted with ether. The organic phase was combined with the filtrate, washed with water, dried over magnesium sulfate, and concentrated to dryness. The residue was purified by column chromatography on silica gel with hexane/20–100% ethyl acetate. Yield: 5.6 g.

Melting point: 172°–174° C. (ethyl acetate).

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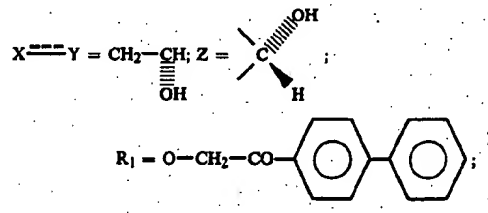
The further reaction steps were conducted analogously to the directions in 1(c)-(g).

Analogously, all other prostaglandin acids and esters described in the present examples can also be converted into the derivatives corresponding to Example 38.

EXAMPLE 39

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic Acid (4-Phenyl)-phenacyl Ester

General Formula I: A=trans—CH=CH; B=cis—CH=CH;



R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

At room temperature, 75 mg. of the prostadienoic acid obtained according to Example 1(f) was agitated with 21 mg. of triethylamine and 53 mg. of p-phenylphenacyl bromide in 4 ml. of acetone for 12 hours under an argon atmosphere. After dilution with water, the reaction mixture was extracted with ether, the ether extract shaken with NaCl solution, dried over magnesium sulfate, and evaporated under vacuum. The residue was filtered over 5 g. of silica gel with ether/dioxan mixtures. Recrystallization from methylene chloride/-hexane yielded 55 mg. of the title compound in the form of colorless crystals.

Melting point: 118° C.

IR: 3600, 1740, 1695, 1590, 1490, 980, 750 cm^{-1}.

In analogy to Example 39, all other prostaglandin acids described in the above examples can be likewise converted to the corresponding phenacyl esters.

EXAMPLE 40

Tris(hydroxymethyl)aminomethane Salt of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic Acid

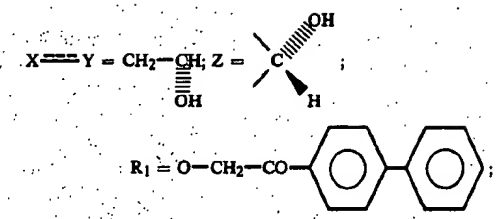
At 60° C., a solution of 32.9 mg. of tris(hydroxymethyl)aminomethane in 0.1 ml. of water was added to a solution of 103 mg. of the prostadienoic acid produced according to Example 1(f) in 14 ml. of acetonitrile. The mixture was allowed to stand at room temperature for 14 hours, thus obtaining 76 mg. of the above salt as colorless crystals.

Analogously to Example 40, all other prostaglandin acids described in the above examples can likewise be converted into the corresponding tris(hydroxymethyl-)aminomethane salts.

EXAMPLE 41

(5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic Acid (4-Phenyl)-phenacyl Ester

General Formula I: A=trans—CH=CH; B=cis—CH=CH;



R_2, R_3, R_4=H; the OH-group on C-15 is in the α-position.

130 mg. of the prostadienoic acid obtained according to Example 5(d) were reacted analogously to Example 39, thus obtaining 85 mg. of the title compound as colorless crystals.

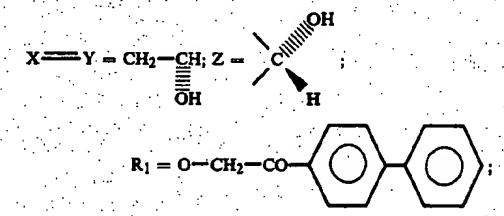
Melting point: 79° C.-80° C.

IR: 3430, 1745, 1695, 1585, 1225, 1030, 760, 750, 720 cm^{-1}.

EXAMPLE 42

(5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanor-prostadienoic Acid (4-Phenyl)-phenacyl Ester

General Formula I: A=trans—CH=CH; B=cis—CH=CH;



R_2, R_3, R_4=H; the OH-group on C-15 is in the β-position.

100 mg. of the prostadienoic acid obtained according to Example 6(c) was reacted analogously to Example 39; thus producing 115 mg. of the title compound in the form of colorless crystals; m.p. 60° C.

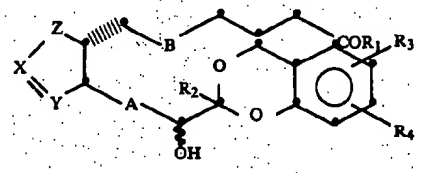
IR: 3440, 1740, 1700, 1590, 1240, 1030, 760, 725 cm^{-1}.

The preceding examples can be repeated with similar success by substituting the generically and specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A 1,3-benzodioxaneprostanoic acid compound of the formula



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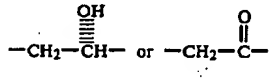
wherein R_1 is (a) hydroxy, (b) alkoxy of 1-10 carbon atoms, (c) methylsulfamido, (d) phenoxy, (e) 1- or 2-naphthoxy, (f) phenoxy or 1- or 2-naphthoxy substituted by 1-3 halogen atoms, phenyl, phenoxy, 1-3 alkyl or alkoxy groups of 1-4 carbon atoms each or one each of chloromethyl, fluoromethyl, trifluoromethyl, carboxy or hydroxy or (g) $O-CH_2-U-V$, wherein U is a direct bond, carbonyl or carbonyloxy, and V is phenyl or phenyl substituted by one or more of phenyl, phenoxy, alkoxy of 1-2 carbon atoms or halogen;

A is $-CH_2-CH_2$ or trans$-CH=CH-$;

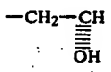
B is $-CH_2-CH_2-$ or cis- or trans$-CH=CH-$;

Z is hydroxymethylene or carbonyl;

X ═══Y, if Z is hydroxymethylene, is



or, if Z is carbonyl, is



or $-CH=CH-$;

R_2 is hydrogen or alkyl of 1-5 carbon atoms;

R_3 and R_4 each are H, F, Cl, Br, I, CF_3, CH_3, or alkoxy of 1-2 carbon atoms or R_3 and R_4 in 6-, 7-position is methylendioxy; and, when R_1 is hydroxy, salts thereof with pharmaceutically acceptable bases.

2. A compound of claim 1, wherein A is $-CH_2CH_2-$.

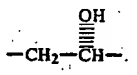
3. A compound of claim 1, wherein A is trans$-CH=CH-$.

4. A compound of claim 1, wherein B is $-CH_2CH_2-$.

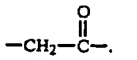
5. A compound of claim 1, wherein B is cis- $-CH=CH-$.

6. A compound of claim 1, wherein B is trans$-CH=CH-$.

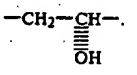
7. A compound of claim 1, wherein Z is hydroxymethylene and X ═══ Y is



8. A compound of claim 1, wherein Z is hydroxymethylene and X ═══Y is



9. A compound of claim 1, wherein Z is carbonyl and X ═══ Y is



10. A compound of claim 1, wherein Z is carbonyl and X═══Y is $-CH=CH-$.

11. A compound of claim 1, wherein R_1 is hydroxy.

12. A compound of claim 1, wherein R_1 is alkoxy of 1-10 carbon atoms.

13. A compound of claim 1, wherein R_1 is methoxy and R_3 and R_4 are H.

14. A compound of claim 1, wherein R_1 is p-phenylphenacyloxy and R_3 and R_4 are H.

15. (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

16. (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

17. (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

18. (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

19. (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

20. (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

21. (5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

22. (5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

23. (5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

24. (5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

25. (5Z,13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

26. (5Z,13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

27. (5Z)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

28. (5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

29. (5Z)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

30. (5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

31. (5Z)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

32. (5Z)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

33. (5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

34. (5Z)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

35. (5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

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36. (5Z)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

37. (5Z)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

38. (5Z)-8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

39. (5Z,10Z,13E)-(8R,12S,15R)-15-Hydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic acid, a compound of claim 1.

40. (5Z,10Z,13E)-(8R,12S,15S)-15-Hydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic acid, a compound of claim 1.

41. (5Z,10Z,13E)-(8R,12S,15R)-15-Hydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic acid, a compound of claim 1.

42. (5Z,10Z,13E)-(8R,12S,15S)-15-Hydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic acid, a compound of claim 1.

43. (5Z,10Z,13E)-(8R,12S,15R)-15-Hydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic acid, a compound of claim 1.

44. (5Z,10Z,13E)-(8R,12S,15S)-15-Hydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostatrienoic acid, a compound of claim 1.

45. (13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

46. (13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

47. (13E)-(8R,9S,11R,15R-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

48. (13E)-(8R,9S,11R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

49. (13E)-(8R,9S,11R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

50. (13E)-(8R,9S,11R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

51. (13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

52. (13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

53. (13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

54. (13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2R}-1,3-benzodioxan-2yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

55. (13E)-(8R,11R,12R,15R)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

56. (13E)-(8R,11R,12R,15S)-11,15-Dihydroxy-9-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostenoic acid, a compound of claim 1.

57. (8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid, a compound of claim 1.

58. (8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid, a compound of claim 1.

59. (8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid, a compound of claim 1.

60. (8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid, a compound of claim 1.

61. (8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid, a compound of claim 1.

62. (8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostanoic acid, a compound of claim 1.

63. (5Z,13E)-(8R,9S,12R,15R)-9,15-Dihydroxy-11-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

64. (5Z,13E)-(8R,9S,12R,15S)-9,15-Dihydroxy-11-oxo-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

65. (5Z,13E)-(8R,9S,12R,15R)-9,15-Dihydroxy-11-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

66. (5Z,13E)-(8R,9S,12R,15S)-9,15-Dihydroxy-11-oxo-15-({2R}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

67. (5Z,13E)-(8R,9S,12R,15R)-9,15-Dihydroxy-11-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

68. (5Z,13E)-(8R,9S,12R,15S)-9,15-Dihydroxy-11-oxo-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

69. (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxane-6-brom-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

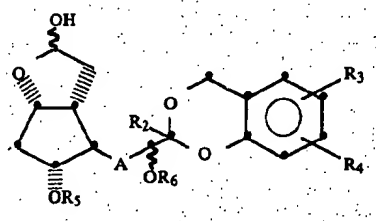
70. (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-Trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid (4-phenyl)-phenacyl ester, a compound of claim 1.

71. Tris(hydroxymethyl)-aminomethane salt of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-trihydroxy-15-({2RS}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

72. (4-Phenyl)-phenacyl ester of (5Z,13E)-(8R,9S,11R,12R,15R)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienioc acid, a compound of claim 1.

73. (4-Phenyl)-phenacyl ester of (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-trihydroxy-15-({2S}-1,3-benzodioxan-2-yl)-16,17,18,19,20-pentanorprostadienoic acid, a compound of claim 1.

74. A lactol of the formula



wherein R_2 is H or alkyl of 1–5 carbon atoms;

R_3 and R_4 each are H, F, Cl, Br, I, CF_3 CH_3 or alkoxy of 1-2 carbon atoms or R_3 and R_4 in 6-, 7-position is methylendioxy;

R_5O— and R_6O— are Oh, acyloxy wherein acyl is the acyl radical of an organic carboxylic acid, or a readily cleavable ether group; and

A is —CH_2CH_2— or trans- —CH=CH—.

75. A pharmaceutical composition comprising a luteolytically effective amount of a compound of claim 1, in admixture with a pharmaceutically acceptable carrier.

76. A method of achieving a luteolytic effect in a patient which comprises administering to the patient a luteolytically effective amount of a compound of claim 1.

* * * * *

United States Patent [19]

Hayashi et al.

[11] **4,128,720**

[45] **Dec. 5, 1978**

[54] **PROSTAGLANDIN ANALOGUES**

[75] Inventors: **Masaki Hayashi; Seiji Kori,** both of Takatsuki; **Hajimu Miyake,** Suita, all of Japan

[73] Assignee: **Ono Pharmaceutical Company,** Osaka, Japan

[21] Appl. No.: **657,125**

[22] Filed: **Feb. 11, 1976**

[30] **Foreign Application Priority Data**

Feb. 14, 1975 [GB] United Kingdom 6385/75

[51] **Int. Cl.**[2] **C07C 177/00**

[52] **U.S. Cl.** ..... **560/9;** 260/327 M; 260/327 C; 562/426; 562/500; 562/503; 260/343.3 P; 260/345.8 P; 536/103; 260/345.7 P; 260/347.2; 260/347.3; 260/347.4; 560/118; 560/121

[58] **Field of Search** 260/516; 560/9

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

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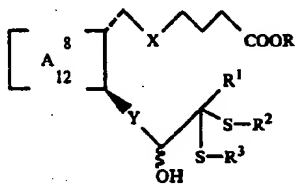
Primary Examiner—Paul J. Killos

Attorney, Agent, or Firm—Albert H. Graddis; Frank S. Chow

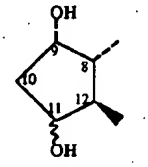
[57] **ABSTRACT**

Prostaglandins of the formula:



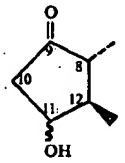
VI

wherein A represents a grouping of the formula:



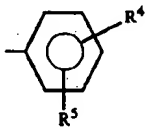
VIIA

or



VIIB

X represents ethylene or cis-vinylene, Y represents ethylene or trans-vinylene, R represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms, R^1 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 10 carbon atoms, R^2 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, R^3 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, a cycloalkyl group containing from 4 to 7 carbon atoms, or a grouping of the formula:



VIII

wherein R^4 and R^5 each represents a hydrogen or halogen atom, a trifluoromethyl group or an alkyl group containing from 1 to 3 carbon atoms, or R^2 and R^3 together represent an ethylene or trimethylene group and cyclodextrin clathrates of such acids and esters and, when R represents a hydrogen atom, non-toxic salts of such acids, are disclosed.

These compounds exhibit characteristic prostaglandin activity, in particular, inhibitory activity on gastric secretion, luteolytic activity and so on.

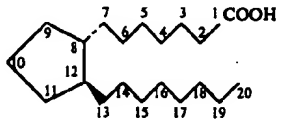
5 Claims, No Drawings

03/03/2003, EAST Version: 1.03.0002

PROSTAGLANDIN ANALOGUES

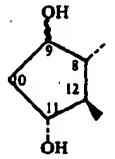
This invention is concerned with new prostaglandin analogues.

Prostaglandins are derivatives of prostanoic acid which has the following formula:



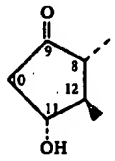
I

Various types of prostaglandins are known, the types depending inter alia on the structure and substituents on the alicyclic ring. For example, the alicyclic rings of prostaglandins F(PGF) and E(PGE) have the structures:



II

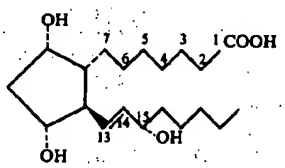
and



III

respectively. In the foregoing formulae and in other formulae throughout this specification the dotted lines denote, in accordance with generally accepted rules of nomenclature, that the attached grouping lies behind the general plane of the ring system, i.e. that the grouping is in α-configuration, the thickened lines denote that the grouping lies in front of the general plane of the system, i.e. that the grouping is in β-configuration, and the wavy line indicates that the grouping is in α- or β-configuration.

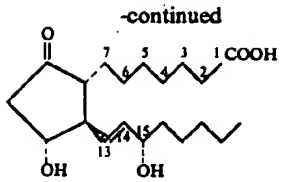
Such compounds are sub-classified according to the position of double bond(s) in the side chain(s) attached to the 8- and 12-positions of the alicyclic ring. Thus PG_1 compounds have a trans-double bond between C_{13}–C_{14}(trans-Δ^{13}) and PG_2 compounds have a cis-double bond between C_5–C_6 and a trans-double bond between C_{13}–C_{14}(cis-Δ^5, trans-Δ^{13}). For example, prostaglandin $F_{1\alpha}$($PGF_{1\alpha}$) and prostaglandin E_1 (PGE_1) are characterized by the following structures IV and V.



IV

and

-continued



V

respectively. The structures of $PGF_{2\alpha}$ and PGE_2, as members of the PG_2 group correspond to those of formulae IV and V respectively with a cis-double bond between the carbon atoms in positions 5 and 6. Compounds in which the double bond between the carbon atoms in positions 13 and 14 of members of the PG_1 group is replaced by ethylene are known as dihydroprostaglandins, e.g. dihydro-prostaglandin-$F_{1\alpha}$ (dihydro-$PGF_{1\alpha}$) and dihydro-prostaglandin-E_1 (dihydro-PGE_1).

Moreover, when one or more methylene groups are added to, or eliminated from, the aliphatic group attached to the 12-position of the alicyclic ring of the prostaglandins the compounds are known, in accordance with the usual rules of organic nomenclature, as homo-prostaglandins (methylene group added) or nor-prostaglandins (methylene group eliminated), and, when more than one methylene group is added or eliminated, the number is indicated by di- tri- etc. before the prefix "homo" or "nor".

Prostaglandins are generally known to possess pharmacological properties, for example they stimulate smooth muscle, have hypotensive, diuretic, bronchodilating and antilipolytic activities, and also inhibit blood platelet aggregation and gastric acid secretion, and are, accordingly, useful in the treatment of hypertension, thrombosis, asthma and gastro-intestinal ulcers, in the induction of labour and abortion in pregnant female mammals, in the prevention of arteriosclerosis, and as diuretic agents. They are fat-soluble substances obtainable in very small quantities from various tissues of animals which secrete the prostaglandins in the living body.

For example, PGEs have an inhibiting effect on gastric acid secretion and may, accordingly, be used in the treatment of gastric ulcers. They also inhibit the release of free fatty acid induced by epinephrine and as a result they reduce the concentration of free fatty acid in blood, and are, accordingly, useful in the prevention of arteriosclerosis and hyperlipemia, PGE_1 inhibits blood platelet aggregation and also removes the thrombus and prevents thrombosis. PGEs and PGFs have a stimulating effect on smooth muscle and increase the intestinal peristalsis; these actions indicate therapeutic utility on post-operative ileus and as purgatives. Furthermore, PGEs and PGFs may be used as oxytocics, as abortifacients in the first and second trimesters; in the post-labour abortion of the placenta, and as oral contraceptives because they regulate the sexual cycle of female mammals. PGEs have vasodilator and diuretic activities. PGEs are useful for improvement in patients suffering from cerebral vascular disease because they increase the cerebral blood flow and are also useful in the treatment of asthmatic conditions in patients because of their bronchodilating activity.

During the past decade widespread investigations have been carried out in order to discover inter alia new products possessing the pharmacological properties of the 'natural' prostaglandins or one or more of such

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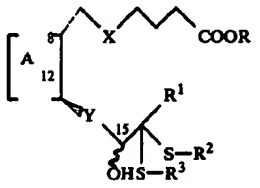
properties to an enhanced degree, or hitherto unknown pharmacological properties. It has now been found that by replacing one of the hydrogen atoms attached to the ≠-position carbon atom in the aliphatic group linked to the 12-position of the alicyclic ring of prostaglandins E and F or analogues thereof by an alkylthio radical and the other hydrogen atom by an alkylthio, cycloalkylthio or phenylthio radical, the pharmacological properties of 'natural' prostaglandins may, in some aspects of their activities, be improved or modified.

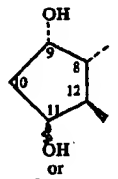
The present invention accordingly provides new prostaglandin analogues of the general formula:

VI



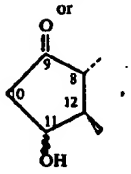
wherein A represents a grouping of the formula:

VIIA



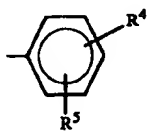
or

VIIB



X represents ethylene (i.e. $—CH_2CH_2—$) or, preferably, cis-vinylene (i.e. —CH=CH—), Y represents ethylene or, preferably, trans-vinylene, R represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms (preferably methyl), R^1 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 10 (preferably 1 to 4) carbon atoms, R^2 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms (preferably methyl), R^3 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, a cycloalkyl group containing from 4 to 7 carbon atoms, or a grouping of the general formula:

VIII



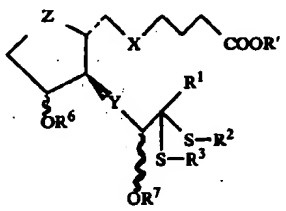
wherein R^4 and R^5 each represents a hydrogen or halogen atom, a trifluoromethyl group or an alkyl group containing from 1 to 3 carbon atoms, or R^2 and R^3 together represent an ethylene or trimethylene group) and cyclodextrin clathrates of such acids and esters and, when R represents a hydrogen atom, non-toxic salts of such acids. Compounds of general formula VI wherein the hydroxy group attached to the 15-position is in the α-configuration are preferred.

The present invention is concerned with all compounds of general formula VI in the 'natural' form or its enantiomeric form, or mixtures thereof, more particularly the racemic form consisting of equimolecular mixtures of natural and its enantiomeric form.

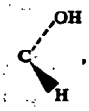
As will be apparent to those skilled in the art, the compounds depicted in general formula VI have at least three centres of chirality, these three centres of chirality being at the alicyclic ring carbon atoms of group A identified as 8 and 12 and at the C-15 carbon atom which has attached to it a hydroxy group. Still further centres of chirality occur when the alicyclic group A carries a hydroxy group on the carbon atom in position 11 (i.e. when the ring is that of formula VIIB) or hydroxy groups in positions 9 and 11 (i.e. when the ring is that of formula VIIA) and further centres of chirality may occur in groups represented by the symbols R^1, R^2 and R^3. The presence of chirality leads, as is well known, to the existence of isomerism. However, the compounds of general formula VI all have such a configuration that the side-chains attached to the ring carbon atoms in the positions identified as 8 and 12 are trans with respect to each other. Accordingly, all isomers of general formula VI, and mixtures thereof, which have those side-chains attached to the ring carbon atoms in positions 8 and 12 in the trans-configuration and have a hydroxy group as depicted in the 15-position are to be considered within the scope of general formula VI.

According to a feature of the present invention, the prostaglandin analogues of general formula VI, wherein R represents a hydrogen atom or a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms, preferably methyl, and the other symbols are as hereinbefore defined, are obtained by the process which comprises hydrolysing a compound of the general formula:

IX



wherein X, Y, R^1, R^2 and R^3 are as hereinbefore defined, Z represents



or C=O, R′ represents a hydrogen atom or a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms, preferably, methyl, and R^6 and R^7 each represent a 2-tetrahydropyranyl group, unsubstituted or substituted by at least one alkyl group, or a 2-tetrahydrofuranyl or 1-ethoxyethyl group, to convert the groups OR^6 and OR^7 to hydroxy groups.

The groups OR^6 and OR^7 of the compounds of general formula IX may be converted to hydroxy groups

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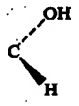
by mild hydrolysis with an aqueous solution of an organic acid, e.g. acetic acid, or with a dilute aqueous inorganic acid, e.g. hydrochloric acid, advantageously in the presence of an organic solvent miscible with water, e.g. tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms, e.g. methanol. The mild hydrolysis may be carried out at a temperature ranging from ambient to 60° C. (preferably at a temperature below 45° C.) with an acid mixture, e.g. a mixture of hydrochloric acid and water with tetrahydrofuran or methanol or a mixture of acetic acid, water and tetrahydrofuran.

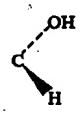
Prostaglandin analogues of general formula VI wherein R represents a straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms can be obtained by reaction of a prostaglandin analogue of general formula VI wherein R represents a hydrogen atom with (i) diazoalkane compounds, e.g. diazomethane, (ii) alcohols in the presence of dicyclohexylcarbodiimide as condensing agent, or (iii) alcohols following the formation of a mixed acid anhydride by adding a tertiary amine and then a pivaloyl halide or an arylsulphonyl or alkylsulphonyl halide (cf. our British Patents Nos. 1362956 and 1364125).

Compounds of general formula IX wherein Z represents C=O may be obtained from compounds of general formula IX wherein Z represents

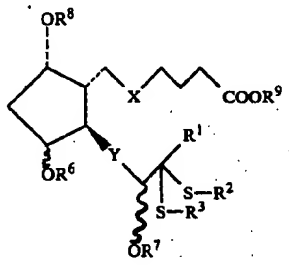


by oxidation under very mild conditions, for example by means of Collins' reagent (chromium trioxide - pyridine complex) at -20° to -50° C. or by means of dimethylsulphide - N-chlorosuccinimide at 0° to -30° C. [cf. E. J. Corey and C. U. Kim, J. Amer. Chem. Soc., 94, 7586 (1972)].

Compounds of general formula IX wherein Z represents



and R′ represents a hydrogen atom may be prepared by reacting a compound of the general formula:



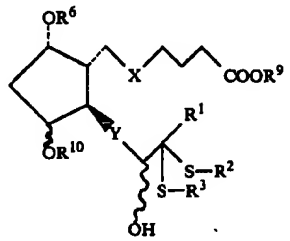
X

(wherein X, Y, R^1, R^2, R^3, R^6 and R^7 are as hereinbefore defined, R^8 represents an alkylcarbonyl group containing from 2 to 5 carbon atoms, and R^9 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms) with an aqueous solution of an alkali metal, e.g. sodium or potassium, hydroxide or carbonate in the presence of a water miscible organic solvent, e.g. tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms.

Compounds of general formula IX wherein Z represents

and R′ represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms may be prepared by reacting a compound of general formula X with anhydrous potassium carbonate in an anhydrous alkanol containing 1 to 4 carbon atoms in a straight- or branched-chain, preferably absolute methanol.

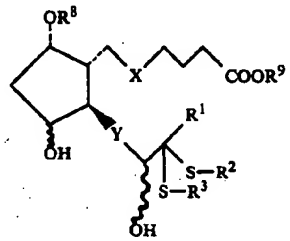
Compounds of general formula X may be prepared by reacting a compound of the general formula:



XI

(wherein X, Y, R^1, R^2, R^3, R^8 and R^9 are as hereinbefore defined and R^{10} represents a hydrogen atom or the group R^6 as hereinbefore defined) with a dihydropyran, dihydrofuran or ethyl vinyl ether in an inert organic solvent, e.g. methylene chloride, in the presence of a condensing agent, e.g. p-toluenesulphonic acid.

Compounds of general formula XI wherein R^{10} represents a hydrogen atom, i.e. compounds of general formula XIA;



XIA

wherein X, Y, R^1, R^2, R^3, R^8 and R^9 are as hereinbefore defined may be prepared by hydrolysing compounds of general formula XI wherein R^{10} represents the group R^6, i.e. compounds of general formula XIB:

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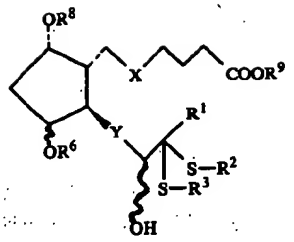
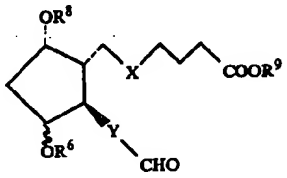
XIB



(wherein X, Y, R^1, R^2, R^3, R^6, R^8 and R^9 are hereinbefore defined) by the methods as hereinbefore described for the conversion of a compound of general formula IX to a compound of general formula VI.

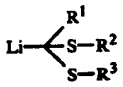
Compounds of general formula XIB may be prepared by the reaction of a compound of the general formula:

XII



(wherein X, Y, R^6, R^8 and R^9 are as hereinbefore defined) with an organolithium compound of the general formula:

XIII

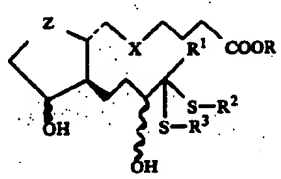


(wherein R^1, R^2 and R^3 are as hereinbefore defined). The reaction is preferably effected at a low temperature, preferably below -30° C., in an inert organic solvent, e.g. diethyl ether, tetrahydrofuran, n-hexane or 1,2-dimethoxyethane, for 10 to 60 minutes. The reaction mixture is then hydrolysed by treatment with water or an aqueous solution of an acid or ammonium chloride to give a mixture of the α- and β-hydroxy epimers of compounds of general formula XIB. It is sometimes possible to separate the isomer having the hydroxy group in α-configuration from the isomer having the hydroxy group in β-configuration by column chromatography of the mixture using silica gel. It is sometimes easier to separate the isomer having the hydroxy group in α-configuration of general formulae XIA and VI from the corresponding isomer having the hydroxy group in β-configuration by column chromatography on silica gel than to separate the isomers of general formula XIB.

According to a further feature of the present invention, compounds of general formula XIA may be directly converted to compounds of the general formula VI wherein A represents a grouping of formula VIIA, R represents a hydrogen atom, and the other symbols are as hereinbefore defined by hydrolysis under alkaline conditions. The hydrolysis is preferably carried out with an aqueous solution of an alkali metal, e.g. sodium or potassium, hydroxide or carbonate in the presence of a water miscible organic solvent, e.g. tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms.

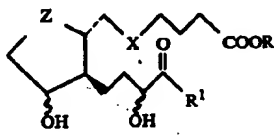
Compounds of general formula VI wherein Y represents an ethylene group, i.e. compounds of the general formula:

VIA



(wherein X, Z, R^1, R^2, R^3 and R are as hereinbefore defined), may be converted to compounds of the general formula:

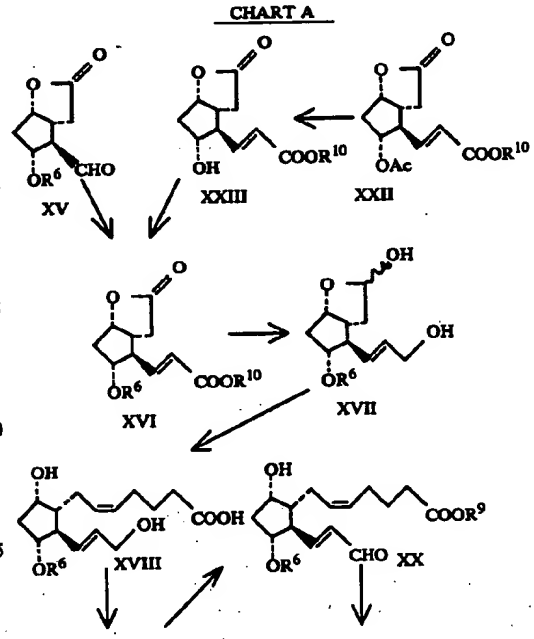
XIV



(wherein X, Z, R^1 and R are as hereinbefore defined) by reaction with N-chlorosuccinimide and silver nitrate in an inert solvent, e.g. water or acetonitrile, at 0° C. to room temperature for 20 to 60 minutes.

The compounds of general formula XII wherein X represents cis-vinylene, Y represents trans-vinylene and R^6, R^8 and R^9 are as hereinbefore defined, hereafter depicted by general formula XII*a*, are prepared by the sequences of reactions hereinafter depicted schematically in Chart A.

CHART A



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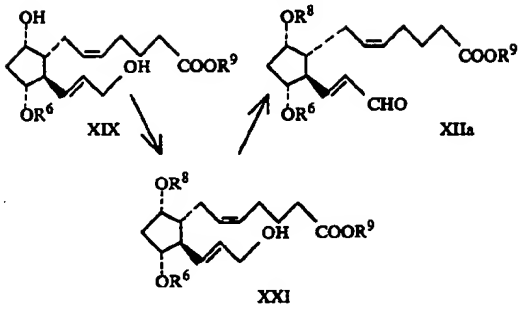
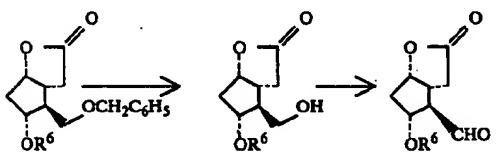
-continued
CHART A



wherein R^{10} represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms, and R^6, R^8 and R^9 are as hereinbefore defined.

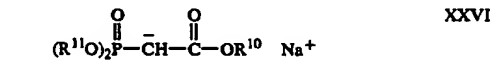
Referring to Chart A, the starting compounds of general formula XV may be prepared from the compounds of general formula XXIV hereafter by the series of reactions depicted schematically below in Chart B, wherein R^6 is as hereinbefore defined.

CHART B



Compounds of general formula XXV may be prepared from compounds of general formula XXIV by catalytic reduction in the presence of a hydrogenation catalyst, for example palladium on charcoal or palladium black, and converted to compounds of general formula XV by oxidation under mild conditions, e.g. with Collins' reagent and at a moderately low temperature.

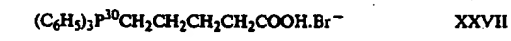
Compounds of general formula XV may be transformed stereospecifically to trans-α, β-unsaturated esters of general formula XVI by reaction with the sodio derivative of compounds of general formula:



(wherein R^{10} is as hereinbefore defined and R^{11} represents an alkyl group containing from 1 to 4 carbon atoms) in an inert organic solvent, e.g. tetrahydrofuran or 1,2-dimethoxyethane, at a temperature of 0° C. to 30° C. for 2 hours, in a high yield, e.g. 70% to 90%.

Compounds of general formula XVI may be converted quantitatively to compounds of general formula XVII by reduction with more than three molar equivalents of diisobutylaluminium hydride in an inert solvent, e.g. toluene, n-pentane or n-hexane, at a low temperature, e.g. -78° C. to -20° C.

Compounds of general formula XVIII may be prepared by the reaction of a compound of general formula XVII with a compound of formula:



in the presence of a strong base, for example sodium methylsulphinylmethylide, under the normal conditions utilized for effecting the Wittig reaction, e.g. in an inert solvent at ambient temperature. The reaction is preferably carried out in dimethyl sulphoxide because the compound of general formula XXVII is practically insoluble in other solvents, e.g. tetrahydrofuran, and because a cis-double bond must be formed stereospecifically in the Wittig reaction. For the better performance of the Wittig reaction, more than three equivalents of the phosphorane compound, prepared from the compound of general formula XXVII, are required. Reaction between the compounds of general formula XVII and the phosphorane is usually completed in about one to five hours at laboratory temperature. The product of formula XVIII, i.e. the acid component of the reaction mixture, may be isolated from the reaction mixture in a high yield by conventional procedures.

Compounds of general formula XVIII may be esterified to obtain compounds of general formula XIX by reaction with (a) appropriate diazoalkane compounds, e.g diazomethane, (b) appropriate alcohols in the presence of dicyclohexyl carbodiimide as condensing agent, or (c) appropriate alcohols following the formation of a mixed acid anhydride by adding a tertiary amine and then a pivaloyl halide or an arylsulphonyl or alkylsulphonyl halide (cf. our British Pats. Nos. 1362956 and 1364125), and then, if desired, converted to compounds of general formula XXI by reaction with trimethylchlorosilane in an inert organic solvent, for example methylene chloride, in the presence of a base, for example pyridine or a tertiary amine, at a low temperature, e.g. at a temperature of -30° C. to 0° C., then reacting the resulting trimethylsilyl ether with the appropriate acyl halide or acid anhydride in an inert organic solvent, for example methylene chloride, in the presence of a base, for example pyridine or a tertiary amine, at a low temperature, e.g. at a temperature of 0° C. to 30° C., and treating the resulting acyl ether by methods known per se for the removal of the trimethylsilyl group, for example by treatment with an acid; it is preferable not to use a strong acid in order to avoid the risk of the removal of the group R^6. By the term "methods known per se" as used in this specification is meant methods heretofore used or described in the chemical literature.

Compounds of general formula XXI may be converted to compounds of general formula XII*a* by oxidation with manganese dioxide, for example in an inert solvent, e.g. methylene chloride, at laboratory temperature, which oxidizes an allylic alcohol group selectively.

Compounds of general formula XII*a* can be prepared from compounds of general formula XIX by oxidation with manganese dioxide, for example in an inert organic solvent, e.g. methylene chloride, at laboratory temperature, and then acylation via compounds of general formula XX.

Compounds of general formula XVI can also be prepared from compounds of general formula XXII by selective deacetylation with an equimolar amount of anhydrous potassium carbonate in absolute methanol and then etherification with a dihydropyran, dihydrofuran or ethylvinyl ether in an inert organic solvent, such as methylene chloride, in the presence of a condensing agent, for example p-toluenesulphonic acid.

Compounds of general formula XXIV may be prepared by known methods, for example as described in J. Org. chem., 37, 2921 (1972) for the preparation of the

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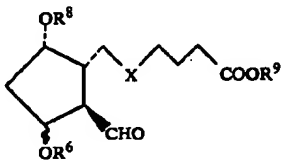
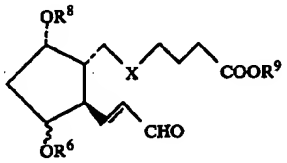
compound of general formula XXIV wherein R^6 is a 2-tetrahydropyranyl group.

Compounds of general formula XII wherein X represents cis-vinylene or ethylene and Y represents trans-vinylene may also be obtained by reaction of a compound of the general formula:



XXVIII

(wherein X, R^6, R^8 and R^9 are as hereinbefore defined) with formylmethylenetriphenylphosphorane in an inert solvent, for example benzene, at about 70° C. for several hours, for example 20 hours, to give compounds of the general formula:



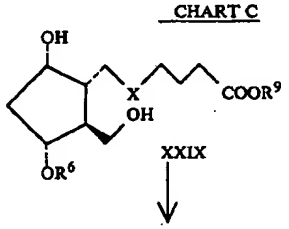
XIIb

wherein X, R^6, R^8 and R^9 are as hereinbefore defined.

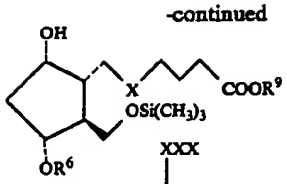
Compounds of general formula XII wherein X and Y represent $-CH_2CH_2-$ may be obtained by reduction of compounds of general formula XII*a* or of general formula XII*b* wherein X represents ethylene by means of diimide, which is prepared from hydrazine and an oxidizing agent, for example hydroperoxide (cf. J. Chem. Ed. 42, 254 (1965)). Compounds of general formula XII wherein X represents cis—CH=CH— and Y represents $-CH_2CH_2-$ may be obtained by the selective reduction of the carbonyl conjugated double bond Y of compounds of general formula XII*a* by methods known per se, for example by means of lithium 1-pentyne-hydrocuprate ($LiCuH—CCC_3H_7$) (see J. Amer. Chem. Soc. 96, 3686 (1974)).

The compounds of general formula XXVIII wherein X, R^6, R^8 and R^9 are as hereinbefore defined and the group OR^6 is in α-configuration [hereinafter depicted in general formula XXVIII*A*], used as starting materials in the hereinbefore described procedure, may themselves be prepared by methods known per se from compounds of general formula XXIX by the series of reactions depicted schematically below in Chart C:

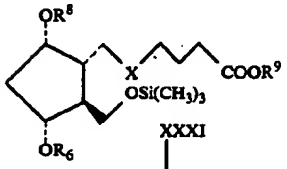
CHART C



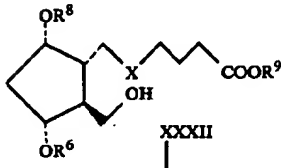
XXIX



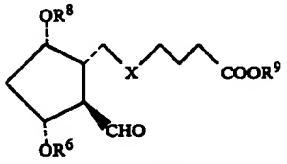
XXX



XXXI



XXXII



XXVIIIA

wherein X, R^6, R^8 and R^9 are as hereinbefore defined, and preferably R^8 represents an acetyl group.

Compounds of formula XXX may be prepared by reacting a compound of formula XXIX with trimethylchlorosilane in an inert organic solvent, for example methylene chloride, in the presence of a base, for example pyridine or a tertiary amine, at a low temperature, e.g. at a temperature of -30° C. to 0° C. Compounds of formula XXXI may be prepared by reacting a trimethylsilyl ether of formula XXX with the appropriate acyl chloride or acid anhydride in an inert organic solvent, for example methylene chloride, in the presence of a base, for example pyridine or a tertiary amine, at a low temperature, e.g. at a temperature of 0° C. to 30° C. Compounds of formula XXXII may be prepared by treating a compound of formula XXXI by methods known per se for the removal of the trimethylsilyl group, for example by treatment with an acid; it is preferable not to use a strong acid in order to avoid the risk of the removal of the group R^6. The compounds of formula XXXII may be converted to compounds of formula XXVIII*A* under mild and neutral conditions, e.g. with chromium trioxide-pyridine complex or Jones ' reagent and at a moderately low temperature.

The compounds of general formula XXIX may themselves be prepared by the method described in Japanese Patent Application No. 48-17416 from the known compounds of formula XXXIII below [the racemic form of the compound of formula XXXIII is described in J. Amer. Chem. Soc. 91, 5675 (1969) and the natural configuration compound of formula XXXIII is described in

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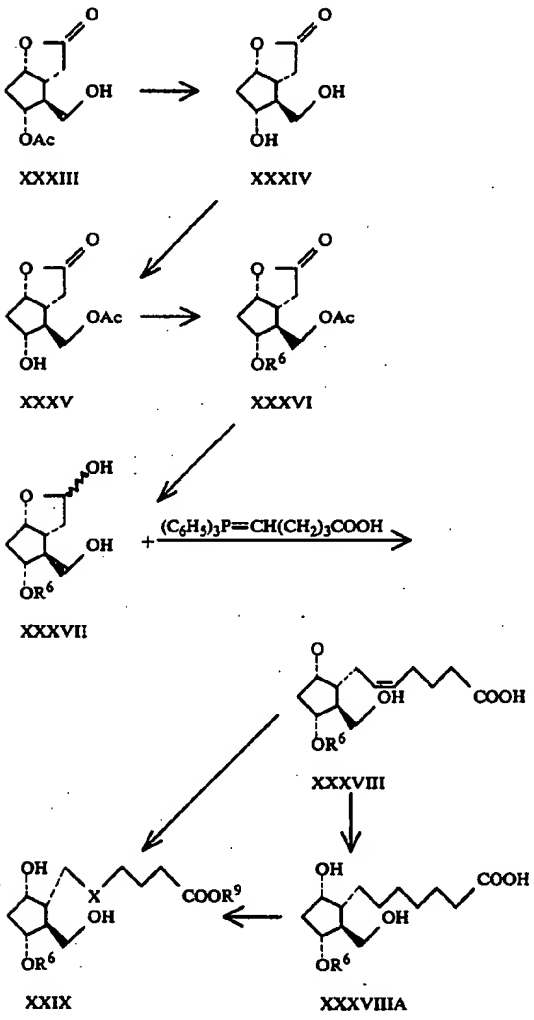
J. Amer. Chem. Soc. 92, 397 (1970)]which may be represented by the series of reactions depicted schematically below in Chart D:-

CHART D

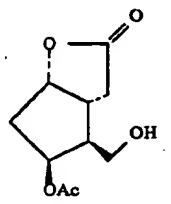


wherein R^6 and R^9 are as hereinbefore defined and Ac represents the acetyl group ($-COCH_3$).

Compounds of formula XXXIV may be prepared by hydrolysis under alkaline conditions of compounds of formula XXXIII. Compounds of formula XXXV may be obtained by the acetylation of compounds of formula XXXIV under mild conditions and may be converted into compounds of formula XXXVI by reaction with a dihydropyran, dihydrofuran or ethyl vinyl ether in an inert solvent, e.g. methylene chloride, in the presence of a condensing agent, e.g. p-toluenesulphonic acid. Compounds of formula XXXVII may be prepared by reducing compounds of formula XXXVI with diisobutylaluminium hydride in toluene for about 15 minutes at -60° C. Dimsyl anion, previously prepared from sodium hydride and dimethyl sulphoxide is reacted with 4-carboxy-n-butyl-triphenylphosphonium bromide to form 4-carboxy-n-butylidenetriphenylphosphorane. To that compound is added a compound of formula XXXVII and the mixture in dimethyl sulphoxide is made to react for 2 hours at room temperature to yield a compound of formula XXXVIII.

Compounds of formula XXXVIII may, if desired, be reduced to give compounds of formula XXXVIIIA. Suitably, the reduction may be effected by hydrogenation in the presence of a hydrogenation catalyst, for example palladium on charcoal, palladium black or platinum dioxide, in the presence of an inert organic solvent, for example a lower alkanol, e.g. methanol or ethanol, at laboratory temperature at normal or elevated pressure, e.g. at a hydrogen pressure from atmospheric to 15 kilogrammes per square centimeter. Compounds of formulae XXXVIII or XXXVIIIA are then reacted with a diazoalkane in a suitable inert solvent, e.g. diethyl ether, to give compounds of formula XXIX.

The compounds of general formula XXVIII wherein X represents cis-vinylene, R^6, R^8 and R^9 are as hereinbefore defined and the group OR^6 is in β-configuration, which may be used as starting materials in the hereinbefore described procedures, may themselves be prepared by the series of reaction depicted in Charts C and D but replacing the compounds of formula XXXIII by compounds of the formula:

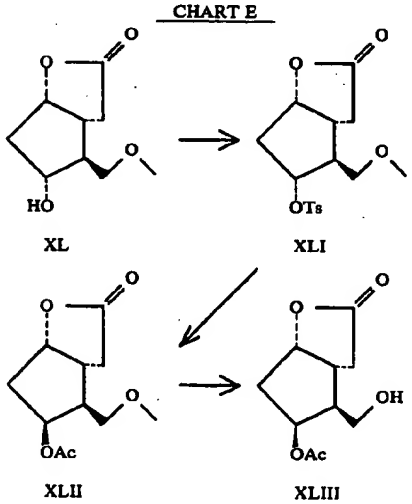


XXXIX

, wherein Ac is as hereinbefore defined.

A method for the preparation of the bicyclo- octane starting materials of formula XXXIX, wherein Ac is as hereinbefore defined, utilizing known procedures may be represented by the series of reactions depicted schematically below in Chart E (cf. E. J. Corney and Shiro Terashima, Tetrahedron Letters, No. 2, pp. 111–113, 1972):

CHART E



wherein Ac is as hereinbefore defined and Ts represents the tosyl group. The various reactions depicted above in Chart E may be effected by methods known per se.

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Compounds of formula XLII may be prepared by reacting compounds of formula XLI with tetraethylammonium acetate.

The prostaglandin analogues of general formula VI wherein R represents a hydrogen atom may, if desired, be converted by methods known per se into salts.

The salts may be prepared, for example, by reaction of stoichiometric quantities of an acid of general formula VI and the appropriate base, e.g. an alakli metal hydroxide or carbonate, ammonium hydroxide or carbonate, ammonia or an amine, in a suitable solvent. The salts may be isolated by lyophilisation of the solution or, if sufficiently insoluble in the reaction medium, by filtration, if necessary after removal of part of the solvent. Preferably the salts are non-toxic salts, i.e. salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the prostaglandins of general formula VI are not vitiated by side-effects ascribable to those cations. Preferably the salts are water-soluble. Suitable salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and pharmaceutically-acceptable (i.e. non-toxic) amine salts. Amines suitable for forming such salts with carboxylic acids are well known and include, for example, amines derived in theory by the replacement of one or more of the hydrogen atoms of ammonia by groups, which may be the same or different when more than one hydrogen atom is replaced, selected from, for example, alkyl groups containing from 1 to 6 carbon atoms and hydroxyalkyl groups containing from 1 to 3 carbon atoms.

The prostaglandins of general formula VI may, if desired, be converted into cyclodextrin clathrates. The clathrates may be prepared by dissolving the cyclodextrin in water and/or an organic solvent which is miscible with water and adding to the solution the prostaglandin compound in a water-miscible organic solvent. The mixture is then heated and the desired cyclodextrin clathrate product isolated by concentrating the mixture under reduced pressure or by cooling and separating the product by filtration or decanting. The ratio of organic solvent to water may be varied according to the solubilities of the starting materials and products. Preferably the temperature is not allowed to exceed 70° C. during the preparation of the cyclodextrin clathrates. α, β-or γ-Cyclodextrins or mixtures thereof may be used in the preparation of the cyclodextrin clathrates. Conversion into their cyclodextrin clathrates serves to increase the stability of the prostaglandin compounds.

The prostaglandin analogues of general formula VI and their cyclodextrin clathrates and, when R in general formula VI represents a hydrogen atom, their non-toxic salts, possess the valuable pharmacological properties typical of prostaglandins, in a selective fashion, including, in particular, inhibitory activity on gastric acid secretion and gastric ulceration, abortifacient activity and stimulatory activity on uterine contraction, luteolytic activity and antinidatory activity and bronchodilator activity at doses which do not, in general, induce diarrhoea as an undesired side-effect, and are useful in the treatment of gastric ulceration, in the termination of pregnancy and induction of labour in pregnant female mammals, in the control of oestrus in female mammals and in the prevention of pregnancy in female mammals, and in the treatment of asthma. For example, in standard laboratory screening tests, (1) in rats in which gastric ulceration was induced by stress according to the method of Takagi and Okabe [Jap. J. Pharmac., 18, 9–18 (1968)], oral administration of 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 methyl ester produces 80.34% and 80.09% inhibitions, respectively, of stress ulceration at doses of 100 and 200 μg./kg. animal body weight, respectively, while oral administration of 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_1 methyl ester produces 57.34% and 85.32% inhibitions, respectively, of stress ulceration at doses of 100 and 200 μg./kg. animal body weight, respectively; (2) when perfused into the stomach of the pentagastrin-treated rat, 16,16-(1,3-dithiapentano)-PGE_2 methyl ester and 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_1 methyl ester produce increases in gastric acid pH from 2.0–2.5 to at least 4.0 in two out of five animals when administered at doses of 10 μg./animal/minute and 0.5–1.0 μg./animal/minute, respectively, and 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 methyl ester produces an increase in gastric acid pH from 2.0–2.5 to at least 4.0 in 50% of pentagastrin-treated rats when administered at a dose of 0.9 (confidence limit 0.54–1.50) μg./animal/minute; (3) when administered intravenously on the 20th day of pregnancy, 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-$PGF_{2\alpha}$, 15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanor-$PGF_{2\alpha}$, 16,16-(1,5-dithiapentano)-$PGF_{2\alpha}$ methyl ester and 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_1 methyl ester stimulate uterine contraction in the pregnant female rat at doses of 5.0–10.0, 10.0–20.0, 20.0–50.0 and 0.5–1 μg./kg. animal body weight, respectively; (4) by subcutaneous administration on the 3rd, 4th and 5th days of pregnancy, 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-$PGF_{2\alpha}$, 16,16-(1,5-dithiapentano)-$PGF_{2\alpha}$methyl ester and 15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanor-$PGF_{2\alpha}$inhibit implantation in pregnant female rats when administered at daily doses of 1.0, 2.0 and 2.0 mg./kg. animal body weight, respectively; (5) when administered intraperitoneally on the 17th day of gestation, 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 methyl ester induces abortion in pregnant female rats when administered twice at a dose of 1.0 mg./kg. animal body weight; (6) after intravenous administration in the anaesthetized guinea pig in which increases in resistance in the respiratory tract were induced by the administration of histamine, as determined by the method of Konzett and Rossler [Arch. exp. Path. Pharmak., 195, 71–74, (1940)], 16,16-(1,3-dithiapentano)-PGE_2 methyl ester produces inhibitions of the histamine induced bronchoconstriction of 35.9% and 22.9%, respectively, at doses of 10.0 and 30.0 μg./kg. animal body weight, respectively, and (7) by inhalation in an aerosol, convulsions induced by the inhalation of a histamine-containing aerosol in the conscious guinea pig are delayed by 16,16-(1,3-dithiapentano)-PGE_2 methyl ester leading to increases in the preconvulsion time of 57%, 11% and 11%, respectively, at doses of 10.0, 100 and 300 μg./ml. of aerosol, respectively, while (8), the doses of 15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanor-PGE_2 methyl ester, 16,16-(1,5-dithiapentano)-PGE_2 methyl ester, 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 ester and 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_1 methyl ester required to produce diarrhoea in 50% of mice (ED_{50}) by oral administration are 8.9, 3.2, 1.43 and 1.2 mg./kg. animal body weight, respectively. The prostaglandin analogues of general formula XIV also possess the valuable pharmacological properties typical of prostaglandins, in a

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selective fashion, including, in particular, hypotensive and bronchodilator activity at doses which do not, in general, induce diarrhoea as undesired side-effect, and are useful in the treatment of hypertension and asthma. For example, in standard laboratory screening tests, 16-oxo-13,14-dihydro-15(ξ)-PGE_1 methyl ester (1) by intravenous administration to the allobarbital-anaesthetized dog, produces falls in blood pressure of 18 mm.Hg and 42 mm.Hg, respectively, lasting 12 minutes and 19 minutes, respectively, at doses of 0.5 and 1.0 μg./kg. animal body weight, respectively; (2) by intravenous administration in the anaesthetized guinea-pig in which increases in resistance in the respiratory tract were induced by the administration of histamine, as determined by the method of Konzett and Rossler [Arch. exp. Path. Pharmak., 195, 71–74 (1940)], produces inhibitions of the histamine induced bronchoconstriction of 23.5%, 68.5% and 84.0%, respectively, at doses of 0.1, 0.5 and 1.0 μg./kg. animal body weight, respectively, while (3), the dose required to produce diarrhoea in 50% of mice (ED_{50}) by oral administration is 8.1 mg./kg. animal body weight.

Preferred compounds of the invention are those compounds of general formula VI wherein R represents a hydrogen atom or a methyl group, R^1 represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms, and R^2 represents an alkyl group containing from 1 to 4 carbon atoms and R^3 represents a phenyl group or R^2 and R^3 together represent an ethylene or trimethylene group.

The following Reference Examples and Examples illustrate the process of the present invention and products thereof. In the Examples 'IR', 'NMR' and 'TLC' represent respectively 'Infrared absorption spectrum', 'Nuclear magnetic resonance spectrum' and 'Thin layer chromatography'. Solvent ratios for chromatographic separations are by volume.

REFERENCE EXAMPLE 1

Phenylthio-methylthio-methane

120 ml. of a 1.3M n-butyllithium solution in n-hexane were added dropwise to a solution of 18.8 ml. of thioanisole in 240 ml. of tetrahydrofuran at −20° C. and the reaction mixture was stirred at that temperature for 2 hours. After cooling to −70° C., 16.4 g. of dimethyldisulphide were added to the reaction mixture, which was then stirred at −70° C. for 15 minutes and at room temperature for 1 hour. The reaction mixture was poured into dilute aqueous hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride and concentrated under reduced pressure. The residue was purified by distillation in vacuo to give 18.0 g. of the title compound having the following physical characteristics:

b.p.: 98 to 102° C./3 mmHg;
IR (liquid film):ν; 2900, 1590, 1200, 750 cm^{-1};
NMR (CCl_4 solution):δ; 7.65–7.10 (5H, m), 3.92 (2H, s), 2.20 (3H, s);
Refractive index: $n_D^{20} = 1.6074$;
Mass spectrum: m/e; 170 (M^+).

REFERENCE EXAMPLE 2

2-Oxa-3-oxo-6-syn-(2-methoxycarbonyl-trans-vinyl)-7-anti-acetoxy-cis-bicyclo[3,3,0]octane

Under an atmosphere of nitrogen and at laboratory temperature, 140 ml. of absolute methylene chloride and 16.1 ml. of absolute pyridine was stirred with 10 g. of chromium trioxide for 30 minutes. 20 g. of infusorial earth were then added to the solution. After cooling the temperature to 0° C., 2.14 g. of 2-oxa-3-oxo-6-syn-hydroxymethyl-7-anti-acetoxy-cis-bicyclo[3,3,0]octane [prepared as described in J. Amer. Chem. Soc., 92, 397 (970)] in 20 ml. of methylene chloride were then added and the mixture stirred for 15 minutes at 0° C. The reaction mixture was then treated with 25 g. of sodium bisulphate and stirred for a further 10 minutes at 0° C. and filtered through a pad of magnesium sulphate. The filtrate was then concentrated under reduced pressure and below 0° C. to give 2-oxo-3-oxo-6-syn-formyl-7-antiacetoxy-cis-bicyclo[3,3,0]octane.

369 mg. of sodium hydride (65% content) were suspended in 60 ml. of absolute tetrahydrofuran. With stirring under an atmosphere of nitrogen at room temperature, 1.82 g. of trimethyl phosphonoacetate [prepared as described in C.R. Acad. Sci. Paris. Ser. A, B 262B, 515 (1966)] were added to the suspension, and stirred for 30 minutes.

The formyl compound, obtained above, in 30 ml. of tetrahydrofuran, was added, whilst maintaining the temperature below 15° C., and stirred for 2 hours at 15° C. Then the reaction mixture was treated with 2 ml. of acetic acid to pH 5 and concentrated slightly. The product was treated with 20 ml. of water and extracted twice with 80 ml. of ethyl acetate (total volume 160 ml.). The organic layer was washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate - benzene (1:4) as eluent to give 2.0 g. of the title compound having the following physical characteristics:

IR (liquid film): ν; 2970, 1775, 1735, 1710, 1650, 1240, 1160, 1037 and 980 cm^{-1};
NMR ($CDCl_3$ solution):δ; 6.77 (1H, d), 5.87 (1H, d), 5.00 (2H, m), 3.70 (3H, s), 3.0–1.9 (6H, m), 2.04 (3H, s);
TLC (developing solvent, ethyl acetate - benzene = 1:2); Rf 32 0.38.

REFERENCE EXAMPLE 3

2-Oxa-3-oxo-6-syn-(2-methoxycarbonyl-trans-vinyl)-7-anti-hydroxy-cis-bicyclo[3,3,0]octane

2.68 g. of 2-oxa-3-oxo-6-syn-(2-methoxycarbonyl-trans-vinyl)-7-anti-acetoxy-cis-bicyclo[3,3,0]octane (prepared as described in Reference Example 2) in 30 ml. of absolute methanol and 1.38 g. of potassium carbonate were stirred at room temperature for 15 minutes, successively cooled in an ice-bath and neutralized with 20 ml. of 1N hydrochloric acid. 260 ml. of ethyl acetate and 27 ml. of an aqueous solution of sodium bicarbonate were added to the reaction mixture and separated into two layers. The organic layer was washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 1.96 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3430, 1786–1690 (broad) and 1650 cm^{-1};
NMR ($CDCl_3$ solution);δ; 6.82 (1H, dd), 5.90 (1H, d), 4.95 (1H, m), 3.72 (3H, s), 4.30–3.25 (2H, m) and 2.90–1.70 (6H, m);
TLC (developing solvent, methylene chloride - methanol = 19:1); Rf = 0.38.

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REFERENCE EXAMPLE 4

2-Oxa-3-oxo-6-syn-(2-methoxycarbonyl-trans-vinyl)-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane

2.31 g. of 2-oxa-3-oxo-6-syn-(2-methoxycarbonyl-trans-vinyl)-7-anti-hydroxy-cis-bicyclo[3,3,0]octane (prepared as described in reference Example 3) were dissolved in 30 ml. of methylene chloride and stirred with 20 ml. of p-toluenesulphonic acid and 3 ml. of dihydropyran for 15 minutes at room temperature. The reaction mixture was neutralized with an aqueous solution of sodium bicarbonate, diluted with ethyl acetate, washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate - benzene (1:3) as eluent to give 3.0 g. of the title compound as white crystals having the following physical characteristics:

m.p. : 85° C.;

IR (KBr tablet):ν; 2930, 1770, 1650, 1343, 1240 and 1152 cm^{-1};

NMR ($CDCl_3$ solution):δ; 6.78 (1H, dd), 5.84 (1H, d), 4.97 (1H, m), 4.63 (1H, m), 3.71 (3H, s) and 4.30–3.20 (3H, m);

TLC (developing solvent, ethyl acetate - benzene = 1:2); Rf = 0.34.

REFERENCE EXAMPLE 5

2-Oxa-3-hydroxy-6-syn-(3-hydroxyprop-trans-1-enyl)-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane

3.10 g. of 2-oxa-3-oxo-6-syn-(2-methoxycarbonyl-trans-vinyl)-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane (prepared as described in Reference Example 4) were dissolved in 100 ml. of toluene and cooled to −65° C. To the solution, 23 ml. of a 25(w/v)% solution of diisobutylaluminium hydride in toluene were added and stirred for 20 minutes at −60° C. Methanol was then added to decompose excess diisobutylaluminium hydride together with water. The precipitate was filtered off and the filtrate was dried and concentrated under reduced pressure to give 2.8 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3390, 2930, 1350 and 1120 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.75–5.15 (3H, m) and 4.75–3.34 (8H, m);

TLC (developing solvent, methylene chloride - methanol = 19:1); Rf = 0.23.

REFERENCE EXAMPLE 6

2α-(6-Methoxycarbonylhex-cis-2-enyl)-3β-(3-hydroxyprop-trans-1-enyl)-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol

2.94 g. of sodium hydride (65% content) were suspended in 40 ml. of dimethyl sulphoxide and stirred with heating at 65° C. for 40 minutes to obtain sodium methyl sulphinylmethylide. The reaction mixture was allowed to cool to room temperature and then added dropwise to a solution of 18.5 g. of (4-carboxybutyl)triphenylphosphonium bromide in 40 ml. of dimethyl sulphoxide, the reaction temperature being kept within the range of 20° C. to 25° C.

A solution of 2.84 g. of 2-oxa-3-hydroxy-6-syn-(3-hydroxy-prop-trans-1-enyl)-7-anti-(2-tetrahydropyranyl-oxy)-cis-bicyclo[3,3,0]octane (prepared as described in Reference Example 5) in 40 ml. of dimethyl sulphoxide was added, and the mixture stirred vigorously at 25° C. for 1 hour. The reaction mixture was poured into 500 ml. of ice-water and neutral substances were removed by extraction with a mixture of ethyl acetate and diethyl ether (1:1). The aqueous layer was acidified to pH 3 with a saturated solution of oxalic acid and extracted with a mixture of diethyl ether and ethyl acetate (1:1). The extracts, after washing with water, were dried over magnesium sulphate and concentrated under reduced presure to give crude 2α-(6-carboxyhex-cis-2-enyl)-3β-(3-hydroxyprop-trans-1-enyl)-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol having the following physical characteristics:

IR (liquid film):ν; 2930, 1720, 1240 and 1120 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.70–5.25 (4H, m) and 4.62 (1H, m);

TLC (developing solvent, methylene chloride - methanol = 19:1); Rf = 0.23.

The crude 6-carboxy compound thus obtained was dissolved in 40 ml. of methylene chloride, cooled to 0° C. nd a solution of diazomethane in diethyl ether was added until the reaction mixture was coloured pale yellow. The reaction mixture was then concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel using a mixture of ethyl acetate - cyclohexane (1:1) as eluent to give 2.87 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3420, 2930, 1740, 1435 and 1020 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.75–5.20 (4H, m), 4.67 (1H, m), 4.20–3.30 (6H, m) and 3.67 (3H, s);

TLC (developing solvent, ethyl acetate - cyclohexane = 2:1); Rf = 0.31.

REFERENCE EXAMPLE 7

2α-(6-Methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol

3.8 g. of active manganese dioxide were added to a solution of 382 mg. of 2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(3-hydroxyprop-trans-1-enyl)-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol (prepared as described in Reference Example 6) in 30 ml. of methylene chloride, the mixture stirred at room temperature for 2 hours and filtered. The precipitate was washed thoroughly with acetone, and the filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate - benzene (1:4) as eluent to give 266 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3450, 2930, 1737, 1688, 1632, 1435, 1125, 1022, and 977 cm^{-1};

NMR ($CDCl_3$ solution):δ; 9.56 (1H, d), 6.82 and 6.79 (1H, dd, respectively), 6.20 and 6.18 (1H, dd respectively), 5.36 (2H, m), 4.58 (1H, m), 3.61 (3H, s) and 4.30–3.20 (4H, m);

TLC (developing solvent, ethyl acetate - benzene = 1:2); Rf = 0.27.

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REFERENCE EXAMPLE 8

1α-Acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane

380 mg. of 2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol (prepared as described in Reference Example 7) were dissolved in 1.61 ml. of pyridine and 1.87 ml. of acetic anhydride were added and stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in 50 ml. of ethyl acetate and 5 ml. of 0.05N hydrochloric acid were added. After separation into two layers, the organic layer was washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate - benzene (1:4) as eluent to give 380 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 2930, 1737, 1687, 1636, 1244, 1127 and 1030 cm^{-1};

NMR ($CDCl_3$ solution):δ; 9.56 (1H, d), 6.82 and 6.79 (1H, each dd), 6.26 and 6.23 (1H, each dd), 5.34 (2H, m), 5.11 (1H, m), 4.56 (1H, m), 4.27–3.25 (3H, m), 3.67 (3H, s), 2.09 (3H, s) and 3.00–1.26 (18H, m);

TLC (developing solvent, ethyl acetate - benzene = 1:2); Rf = 0.50.

REFERENCE EXAMPLE 9

Methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate

10 ml. of a 1.4M solution of n-butyllithium in n-hexane were added dropwise to a solution of 2.0 ml. of phenylthio-methylthio-methane (prepared as described in Reference Example 1) in 15 ml. of tetrahydrofuran under an atmosphere of nitrogen at −20° C. and the reaction mixture was stirred at the same temperature for 2 hours. 17.8 ml. of the reaction mixture thus obtained were added dropwise at −70° C. to a solution of 2.7 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 8) in 50 ml. of tetrahydrofuran and the reaction mixture was stirred at the same temperature for 1 hour and at 0° C. for a further 30 minutes, poured into dilute aqueous hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene - ethyl acetate as eluent to give 2.84 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3450, 1730, 1590, 1430, 1250, 980 cm^{-1};

NMR ($CDCl_3$ solution):ν; 7.65–7.15 (5H, m), 5.85–4.90 (5H, m), 4.90–4.50 (1H, m), 3.65 (3H, s), 2.25 (1.5H, s), 2.21 (1.5H, s), 2.05 (3H, s).

EXAMPLE 1

Methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate

2.75 g. of methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 9) were dissolved in a mixture of 40 ml. of tetrahydrofuran and 10 ml. of 1N hydrochloric acid and the reaction mixture was stirred at 40° C. for 2 hours and then extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene - ethyl acetate as eluent to give 810 mg. of the title compound, having the following physical characteristics, 655 mg. of the 15β-hydroxy isomer and 510 mg. of a mixture of them:

TLC (developing solvent, benzene - ethyl acetate = 1:2); Rf = 0.19 (Rf of the 15β-hydroxy isomer = 0.29);

IR (liquid film):ν; 3400, 1730, 1590, 1250, 980 cm^{-1};

NMR ($CDCl_3$ solution):δ; 7.70–7.15 (5H, m), 5.90–4.90 (5H, m), 3.65 (3H, s), 2.25 (1.5H, s), 2.21 (1.5H, s), 2.05 (3H, s).

EXAMPLE 2

9α,11α,15α-Trihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoic acid [16(ξ)-Phenylthio-16-methylthio-17,18,19,20-tetranor-$PGF_{2\alpha}$]

A solution of 130 mg. of potassium hydroxide in 3 ml. of water was added to a solution of 238 mg. of methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate (prepared as described in Example 1) in 4 ml. of ethanol, and the reaction mixture was stirred at room temperature for 1.5 hours, then acidified to pH 2 to 3 with an aqueous solution of acetic acid and extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate - cyclohexane as eluent to give 140 mg. of the title compound having the following physical characteristics:

TLC (developing solvent, chloroform - tetrahydrofuran - acetic acid = 10:2:1); Rf = 0.13;

IR (liquid film):ν; 3360, 1710, 1580, 1250, 980 cm^{-1};

NMR ($CDCl_3$ solution):δ; 7.60–7.20 (5H, m), 5.80–5.55 (2H, m), 5.55–5.25 (2H, m), 4.88 (4H, broad s), 4.40–3.85 (4H, m), 2.24 (1.5H, s), 2.20 (1.5H, s).

REFERENCE EXAMPLE 10

Methyl 9α-acetoxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate

10 mg. of p-toluenesulphonic acid and 427 mg. of 2,3-dihydropyran were added to a solution of 400 mg. of

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methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate (prepared as described in Example 1) in 10 ml. of methylene chloride and the reaction mixture was stirred at room temperature for 20 minutes and then poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene - ethyl acetate as eluent to give 500 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 1730, 1580, 1435, 1250, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.70–7.15 (5H, m), 5.90–4.90 (5H, m), 4.90–4.50 (2H, m), 3.64 (3H, s), 2.25 (3H, s), 2.05 (3H, s).

EXAMPLE 3

Methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate

A solution of 500 mg. of methyl 9α-acetoxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 10) in 7 ml. of methanol was stirred with 122 mg. of anhydrous potassium carbonate at 50° C. for 2 hours. The reaction mixture was poured into dilute aqueous hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 470 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3400, 1730, 1580, 1435, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.70–7.10 (5H, m), 5.80–5.15 (4H, m), 4.95–4.50 (2H, m), 3.60 (3H, s), 2.24 (3H, s).

EXAMPLE 4

Methyl 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate

0.648 ml. of dimethylsulphide was added to a solution of 495 mg. of N-chlorosuccinimide in 15 ml. of toluene at −20° C. After stirring for 1 hour, a solution of 470 mg. of methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate (prepared as described in Example 3) in 10 ml. of toluene was added and the reaction mixture was stirred at −20° C. for 2 hours. Then a solution of 0.923 ml. of triethylamine in 1.3 ml. of n-pentane was added to the reaction mixture, which was stirred at room temperature for 10 minutes, diluted with ethyl acetate, washed with aqueous hydrochloric acid, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate as eluent to give 329 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 1740, 1580, 1440, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.70–7.15 (5H, m), 5.95–5.20 (4H, m), 4.90–4.50 (2H, m), 3.65(3H, s), 3.00–2.50 (1H, m), 2.26 (3H, s).

EXAMPLE 5

Methyl 9-oxo-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate [16(ξ)-Phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 methyl ester]

327 mg. of methyl 9 -oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate (prepared as described in Example 4) were dissolved in a mixture of 1 ml. of tetrahydrofuran and 6.7 ml. of a 65% aqueous solution of acetic acid and the reaction mixture was stirred at 40° C. for 2 hours and then extracted with ethyl acetate. The extracts were washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and cyclohexane as eluent to give 153 mg. of the title compound having the following physical characteristics:

TLC (developing solvent, chloroform - tetrahydrofuran - acetic acid = 10:2:1); Rf = 0.53;

IR (liquid film): ν; 3400, 1735, 1580, 1435, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.60–7.25 (5H, m), 5.90–5.70 (2H, m), 5.53–5.25 (2H, m), 4.45–3.95 (3H, m), 3.65 (3H, s), 3.80–3.30 (2H, m), 2.90–2.58 (1H, m), 2.27 (1.5H, s), 2.24 (1.5H, s).

REFERENCE EXAMPLE 11

1α-Acetoxy-2α-(6-methoxycarbonylhexyl)-3β-formyl-4α-(2-tetrahydropyranyloxy)-cyclopentane

700 mg. of 5% palladium on carbon were suspended in 30 ml. of methanol, the air in the apparatus was replaced by hydrogen, and a solution of 2.0 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-formyl-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described hereinafter) in 10 ml. of methanol was added thereto. Catalytic reduction of the compound was carried out at room temperature under ambient pressure for 10 minutes. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 1.95 g. of the title compound having the following physical characteristics:

IR (liquid film): ν; 2930, 1740, 1440, 1250, 1030 cm^{-1};

NMR ($CDCl_3$ solution): δ; 9.66 (1H, t), 5.25–4.90 (1H, m), 3.65 (3H, s), 2.06 (3H, s).

1α-Acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-formyl-4α-(2-tetrahydropyranyloxy)-cyclopentane, used as a starting material in the above procedure, may be prepared from 2-oxa-3-oxo-6-syn-hydroxymethyl-7-antiacetoxy-cis-bicyclo[3,3,0]octane, [prepared as described by E. J. Corey et al., J. Am. Chem. Soc., 92, 397, (1970)], as follows:

190 g. of 2-oxa-3-oxo-6-syn-hydroxymethyl-7-anti-acetoxy-cis-bicyclo[3,3,0]octane in 1.5 liters of absolute methanol and 130 g. of potassium carbonate were stirred at room temperature for 1 hour, and then successively cooled in an ice-bath, and neutralized with hydrochloric acid. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The

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residue was washed with ethanol, and then with ethyl acetate, and dried to give 124 g. of 2-oxa-3-oxo-6-syn-hydroxymethyl-7-anti-hydroxy-cis-bicyclo[3,3,0]octane as white crystallites having the following physical characteristics:

m.p. : 119° C.;

IR (KBr tablet): ν; 3350, 2970–2880, 1740, 1480, 1440, 1410, 1380, 1335, 1305, 1270, 1205, 1100, 1080, 1060, 1040, 1020, 1000 and 975 cm^{-1};

NMR (in $CDCl_3$ + deutero dimethyl sulphoxide solution): δ; 5.10–4.60 (1H, m), 4.29 (2H, s), 4.13–3.77 (1H, m) and 3.38 (2H, d);

TLC (developing solvent, methylene chloride - methanol = 20:1); Rf = 0.27.

124 g. of 2-oxa-3-oxo-6-syn-hydroxymethyl-7-anti-hydroxy-cis-bicyclo[3,3,0]octane, obtained as described above, were dissolved in absolute pyridine (1.4 liters) and cooled to −40° C. 74 g. of acetic anhydride were added dropwise and the mixture stirred for 5 hours at −40 to −20° C. and then for 16 hours at 0° C. The pyridine was evaporated off under reduced pressure and the residue was dissolved in 1 liter of ethyl acetate. 200 g. of sodium bisulphate were added, and the solution was stirred vigorously and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (1:3) as eluent to give 112 g. of 2-oxa-3-oxo-6-syn-acetoxymethyl-7-anti-hydroxy-cis-bicyclo[3,3,0]octane as colourless needles having the following physical characteristics:

m.p. : 36–37° C.;

IR (KBr tablet): ν; 3450, 2960, 2850, 1775, 1740, 1420, 1370, 1250, 1190, 1120, 1090, 1040 and 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 5.15–4.60 (1H, m), 4.3–3.75 (3H, m), 3.50 (1H, s) and 2.02 (3H, s);

TLC (developing solvent, methylene chloride - methanol = 20:1); Rf =0.50.

4.3 g. of 2-oxa-3-oxo-6-syn-acetoxymethyl-7-anti-hydroxy-cis-bicyclo[3,3,0]octane, obtained as described above, were dissolved in 520 ml. of methylene chloride, 25 g. of dihydropyran and 0.52 g. of p-toluenesulphonic acid were added and the mixture stirred for 20 minutes at room temperature. The reaction mixture was neutralized with an aqueous solution of sodium bicarbonate, diluted with ethyl acetate, washed with water, dried and concentrated under reduced pressure to give 56 g. of 2-oxa-3-oxo-6-syn-acetoxymethyl-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane as a colourless oil having the following physical characteristics:

IR (liquid film): ν; 2950–2840, 1775, 1740, 1465, 1440, 1390–1340, 1240, 1180, 1140–1120, 1080, 1040 and 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 5.2–4.72 (1H, m), 4.72–4.30 (1H, m), 4.2–3.2 (5H, m) and 2.01 (3H, s);

TLC (developing solvent, methylene chloride-methanol = 20:1); Rf = 0.74.

56 g. of the acetyl ether, prepared as described above, were dissolved in 900 ml. of toluene and cooled to −60° C. 456 ml. of a 25(w/v)% solution of diisobutylaluminium hydride in toluene were added, and the solution was stirred for 20 minutes at the same temperature; methanol was added in order to decompose the excess of diisobutylaluminium hydride and water was added. The resulting precipitate was filtered off and the filtrate was dried and concentrated under reduced pressure to give 35.2 g. of 2-oxa-3-hydroxy-6-syn-hydroxymethyl-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane as a colourless oil having the following physical characteristics:

IR (liquid film); ν; 3400, 2940–2860, 1465–1440, 1380, 1355, 1325, 1260, 1200, 1140, 1120, 1075 and 1020 cm^{-1};

TLC (developing solvent, ethyl acetate); Rf = 0.25.

37.6 g. of sodium hydride (content 63.5%) were suspended in 400 ml. of dimethyl sulphoxide and stirred at 70° C. for 1.5 hours to obtain sodium methylsulphinylmethylide. The reaction mixture was allowed to cool to room temperature and then added dropwise to a solution of 226 g. of (4-carboxybutyl)triphenylphosphonium bromide in 460 ml. of dimethyl sulphoxide, the reaction temperature being kept within the range 20 to 25° C.

A solution of 35.2 g. of 2-oxa-3-hydroxy-6-syn-hydroxymethyl-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane, prepared as described above, in 90 ml. of dimethyl sulphoxide was added to the above reaction mixture and stirred at 35 to 40° C. for 1.5 hours. The reaction mixture was poured into 6 liters of ice-water and the neutral substances were removed by extraction with an ethyl acetate-diethyl ether mixture (1:1). The aqueous layer was acidified to pH 2 with a saturated aqueous solution of oxalic acid and extracted with a diethyl ether-n-pentane mixture (1:1). The organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a mixture of benzene and methanol (10:1) as eluent to give 35 g. of 2α-(6-carboxyhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol as a colourless oil having the following physical characteristics:

(liquid film): ν; 3400, 2940–2860, -2300, 1710, 1450, 1435, 1400, 1355, 1245, 1200, 1140, 1120, 1075 and 1025 cm^{-1};

NMR (in $CDCl_3$ solution): δ; 6.20 (3H, s), 5.50–5.10 (2H, m), 4.75–4.36 (1H, m), 4.24–3.85 (2H, m) and 3.85–3.0 (4H, m);

TLC (developing solvent, chloroform - tetrahydrofuran - acetic acid = 10:2:1); Rf = 0.53.

To a solution of 18.8 g. of 2α-(6-carboxyhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol, obtained as described above, in 130 ml. of diethyl ether, a freshly prepared ethereal solution of diazomethane was added with cooling in an ice-bath until the reaction mixture showed a pale yellow colour. The reaction mixture was concentrated in vacuo, and the residue was subjected to column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (2:1) as eluent to give 15.4 g. of 2α-(6-methoxycarbonyl-hex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol as a colourless oil having the following physical characteristics:

IR (liquid film): ν; 3450, 2950, -2870, 1740, 1440, 1360, 1325, 1250, 1200, 1140, 1120, 1080 and 1025 cm^{-1};

NMR (in $CDCl_3$ solution): δ; 5.55–5.00 (2H, m), 4.78–4.30 (1H, m), 4.20–3.06 (6H, m), 3.55 (3H, s) and 2.97 (2H, s);

TLC (developing solvent, methylene chloride - methanol = 19:1); Rf = 0.43.

13.1 g. of 2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentan-1α-ol, obtained as described above, were dissolved in 250 ml. of absolute methylene chloride, and 25 ml. of pyridine were added. The air in the apparatus was replaced with nitrogen and the contents cooled to −20° C. To the reaction mixture was added dropwise a solu-

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tion of 5.1 ml. of trimethylchlorosilane in 30 ml. of methylene chloride with stirring and the mixture was then stirred at the same temperature for 30 minutes. A sample of the product thus obtained had the following physical characteristic:

TLC (developing solvent, benzene - ethyl acetate = 2:1); Rf = 0.61.

A solution of 2.9 ml. of acetyl chloride in 20 ml. of methylene chloride was added dropwise to the above reaction mixture and stirred at room temperature for 30 minutes. Then 2 ml. of ethanol were added to decompose the excess of acetyl chloride. Pyridine in the reaction mixture was neutralized by the addition of 50 g. of sodium bisulphate, and the resulting precipitate was filtered off. The filtrate was concentrated under reduced pressure to give a residue having the following physical characteristic:

TLC (developing solvent, benzene - ethyl acetate = 2:1); Rf = 0.82.

The residue was dissolved in 300 ml. of ethyl acetate, 100 ml. of an aqueous solution of oxalic acid were added and the solution was stirred vigorously at room temperature. The organic layer was separated, washed successively with water, an aqueous solution of sodium bisulphate, water and an aqueous solution of sodium chloride, dried with sodium sulphate and concentrated under reduced pressure to give 13.7 g. of crude product. The crude product was subjected to column chromatography on silica gel using a mixture of benzene and ethyl acetate (3:1) as eluent to give 7.45 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentane, 2.40 g. of 1α-hydroxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentane, 720 mg. of 1α-hydroxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-acetoxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentane, and 1.45 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-acetoxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentane.

1α-Acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentane had the following physical characteristics:

IR (liquid film): ν; 3450, 3000, 2950, 2870, 1740, 1440, 1380, 1330, 1250, 1200, 1160, 1140, 1080, 1030, 980, 920, 875 and 815 cm^{-1};

NMR (in $CDCl_3$ solution): δ; 5.45–5.27 (2H, m), 5.16–4.92 (1H, m), 4.76–4.46 (1H, m), 4.27–3.96 (1H, m), 3.67 (3H, s), 2.98–2.64 (1H, m) and 2.05 (3H, s);

TLC (developing solvent, benzene - ethyl acetate = 2:1); Rf = 0.27.

Under an atmosphere of nitrogen, 4.4 ml. of pyridine were dissolved in 80 ml. of methylene chloride, 2.88 g. of chromium trioxide were added with stirring and the solution was stirred for 15 minutes. 12 g. of infusorial earth were added to the reaction mixture, and then there was added a solution of 956 mg. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-hydroxymethyl-4α-(2-tetrahydropyranyloxy)-cyclopentane, prepared as described above, in 20 ml. of methylene chloride. After stirring for 10 minutes, 20 g. of sodium bisulphate were added to the reaction mixture and stirring continued for a further 10 minutes. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a mixture of benzene and ethyl acetate (5:1) as eluent to give 1α-acetoxy-2α- (6-methoxycarbonylhex-cis-2-enyl)-3β-formyl-4α-(2-tetrahydropranyloxy)cyclopentane as a colourless oil having the following physical charcteristics:

IR (liquid film): ν; 3000, 2950, 2860, 2725, 1740, 1440, 1380, 1325, 1255, 1200, 1165, 1140, 1085, 1030, 980, 920, 880 and 820 cm^{-1};

NMR (in $CDCl_3$ solution): δ; 9.85–9.68 (1H, m), 5.45–4.96 (1H, m), 4.68–4.48 (1H, m), 4.48–4.25 (1H, m), 3.67 (3H, s) and 2.08 (3H, s);

TLC (developing solvent, benzene - ethyl acetate = 2:1); RF = 0.66.

REFERENCE EXAMPLE 12

1α-Acetoxy-2α-(6-methoxycarbonylhexyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane

1.95 g. of 1α-acetoxy-2α-(6-methoxycarbonylhexyl)-3β-formyl-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 11) and 1.57 g. of formylmethylenetriphenylphosphorane (prepared as described in J. Chem. Soc., 1961, 1268) were dissolved in 25 ml. of dry benzene and the solution was stirred at 70° C. for 20 hours. The reaction mixture was then purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate as eluent to give 1.73 g. of the title compound having the following physical characteristics:

IR (liquid film): ν; 1740, 1690, 1640, 1440, 1250, 1030 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.00–5.90 (2H, m), 5.30–4.90 (1H, m), 4.70–4.40 (1H, m), 3.65 (3H, s), 2.06 (3H, s).

REFERENCE EXAMPLE 13

Methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate

By proceeding as described in Reference Example 9 but utilising 13.2 ml. of the reaction mixture obtained from 7.5 ml. of a 1.4M solution of n-butyl- lithium in n-hexane and a solution of 1.5 ml. of phenylthio-methylthio-methane in 11 ml. of tetrahydrofuran and replacing the 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)cyclopentane by 1.7 g. of 1α-acetoxy-2α-(6-methoxycarbonylhexyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 12) in 35ml. of tetrahydrofuran there were obtained 2.0 g. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3450, 1740, 1590, 1430, 1250, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.65–7.15 (5H, m), 5.80–5.50 (2H, m), 5.20–4.90 (1H, m), 4.90–4.50 (1H, m), 3.65 (3H, s), 2.25 (1.5H, s), 2.21 (1.5H, s), 2.05 (3H, s).

EXAMPLE 6

Methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate

By proceeding as described in Example 1 but replacing the methyl 9α-acetoxy-11α-(2 -tetrahydropyranyloxy)-15(ξ)-hydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate by 2.0 g. of methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16(ξ)-phenylthio-16-

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methylthio-17,18,19,20-tetranorprost-trans-13-enoate (prepared as described in Reference Example 13) and utilising a mixture of 30 ml. of tetrahydrofuran and 7 ml. of 1N hydrochloric acid there were obtained 475 mg. of the title compound, having the following physical characteristics, 490 mg. of the 15β-hydroxy isomer and 230 mg. of a mixture of them:

TLC (developing solvent, benzene - ethyl acetate = 1:2); Rf = 0.20, (Rf of the 15β-hydroxy isomer = 0.30);

IR (liquid film): ν; 3400, 1740, 1710, 1590, 1250, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.60–7.05 (5H, m), 5.75–5.45 (2H, m), 5.30–4.90 (1H, m), 3.62 (3H, s), 2.25 (1.5H, s), 2.21 (1.5H, s), 2.05 (3H, s).

REFERENCE EXAMPLE 14

Methyl 9α-acetoxy-11α,15α-bis-(2-tetrahydropranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate

By proceeding as described in Reference Example 10 but replacing the methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate by 375 mg. of methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate (prepared as described in Example 6) dissolved in 8 ml. of methylene chloride, and utilising 7 mg. of p-toluenesulphonic acid and 0.34 ml. of 2,3-dihydropyran there were obtained 420 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 1740, 1590, 1440, 1250, 1030 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.60–7.00 (5H, m), 5.80–5.40 (2H, m), 5.20–4.90 (1H, m), 4.90–4.50 (2H, m), 3.61 (3H, s), 2.23 (3H, s), 2.02 (3H, s).

EXAMPLE 7

Methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydrpyranyloxy)-18 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate

By proceeding as described in Example 3 but replacing the methyl 9α-acetoxy-11α15α-bis-(2-tetrahydropranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate by 420 mg. of methyl 9α-acetoxy-11α,15α-bis-(2-tetrhydropranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate (prepared as described in Reference Example 14) dissolved in 6 ml. of methanol and utilising 103 mg. of anhydrous potassium carbonate there were obtained 395 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3450, 1740, 1440, 1030, 980 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.60–7.00 (5H, m), 5.80–5.45 (2H, m), 4.90–4.50 (2H, m), 3.62 (3H, s), 2.23 (3H, s).

EXAMPLE 8

Methyl 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranoroprost-trans-13-enoate

By proceeding as described in Example 4 but utilising 0.543 ml. of dimethylsulphide and a solution of 414 mg. of N-chlorosuccinimide in 13 ml. of toluene, replacing the methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-[5,trans-13-dienoate by 395 mg. of methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate (prepared as described in Example 7) dissolved in 9 ml. of toluene and utilising a solution of 0.78 ml. of triethylamine in 1.1 ml. of n-pentane there were obtained 235 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 1740, 1710, 1590, 1440, 1030 cm^{-1};

NMR ($CDCl_3$ solution):δ; 7.60–7.10 (5H, m), 5.95–5.55 (2H, m), 4.85–4.50 (2H, m), 3.62 (3H, s) 2.25 (3H, s).

EXAMPLE 9

Methyl 9-oxo-11αα,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprost-trans-13-enoate [16(ξ)-Phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_1 methyl ester]

By proceeding as described in Example 5 but replacing the methyl 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate by 285 mg. of methyl 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio- 16-methylthio-17,18,18,20-tetranorprost-trans-13-enoate (prepared as described in Example 8) and utilising a mixture of 0.9 ml. of tetrahydrofuran and 5.8 ml. of a 65% aqueous solution of acetic acid there were obtained 150 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3400, 1740, 1590, 1440, 980 cm^{-1};

NMR ($CDCl_3$ solution):δ; 7.60–7.25 (5H, m), 5.90–5.70 (2H, m), 4.20–3.95 (2H, m), 3.65 (3H, s), 3.50–3.20 (2H, m), 2.90–2.58 (1H, m), 2.27 (1.5H, s), 2.24 (1.5H, s);

TLC (developing solvent, ethyl acetate); Rf = 0.50.

REFERENCE EXAMPLE 15

Methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15α-hydroxy-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate

13.2 ml. of a 0.5M solution of n-butyllithium in n-hexane were added dropwise to a solution of 720 mg. of 1,3-dithiane in 25 ml. of anhydrous tetrahydrofuran under an atmosphere of nitrogen at −25° C. and the reaction mixture was stirred for 2 hours to give lithio-1,3-dithiane. 2.028 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 8) were dissolved in 20 ml. of tetrahydrofuran, cooled to a temperature below -60° C. and, under an atmosphere of nitrogen, the lithio-1,3-dithiane solution, obtained above, was added slowly. the reaction mixture was stirred for 40 minutes and then acidified with 2ml. of acetic acid. After evaporation of the solvent under reduced pressure, the residue was dissolved in ethyl acetate, washed with water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was separated and purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (4:1) as eluent to give 852 mg. of the title compound, having the following physical characteristics,

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604 mg. of the 15β-hydroxy isomer and 594 mg. of the starting formyl compound:

IR (liguid film):ν; 3440, 2940, 2900, 2865, 1730, 1435, 1380, 1360, 1330, 1250, 1175, 1140, 1085, 1030, 975, 920, 875 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.90–5.60 (2H, m), 5.55–5.20 (2H, m), 5.20–4.85 (1H, m), 4.85–4.50 (1H, m), 4.50–3.15 (8H, m), 3.15–2.65 (4H, m), 2.05 (3H, s);

TLC (developing solvent, benzene - ethyl acetate = 1:1);

Rf = 0.53, (Rf of 15β-hydroxy isomer = 0.59).

REFERENCE EXAMPLE 16

Methyl 9α-acetoxy-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate

1.48 g. of methyl 9α-acetoxy11α-(2-tetrahydropyranyloxy)-15α-hydroxy-15-[2-(1,3-dithiacyclohexy)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 15) were dissolved in 15 ml. of methylene chloride and the solution was reacted with 0.5 ml. of 2,3-dihydropyran and 8 mg. of p-toluenesulphonic acid at room temperature for 15 minutes. The reaction mixture was diluted with ethyl acetate, washed with an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure to give 1.7 g. of the title compound having the following physical characteristics:

IR (liquid film;ν; 2940, 2860, 1740, 1455, 1440, 1385, 1355, 1315, 1250, 1200, 1185, 1160, 1130, 1080, 1040, 1030, 975, 920, 875 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.00–5.20 (4H, m), 5.20–4.80 (1H, m), 4.80–4.45 (2H, m), 4.45–3.15 (10H, m), 3.15–2.65 (4H, m), 2.05 (3H, s);

TLC (developing solvent, benzene - ethyl acetate = 2:1);

Rf = 0.62.

EXAMPLE 10

9α-Hydroxy-11α,15α-bis(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorporosta-cis-5,trans-13-dienoic acid

660 mg. of methyl 9α-acetoxy-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 16) were dissolved in a mixture of 2 ml. of 4N potassium hydroxide and 7 ml. of methanol and the solution stirred at toom temperture for 1 hour. The reaction mixture was acidified with an aqueous solution of oxalic acid and extracted with ehtyl acetate. The organic extracts were washed with water and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure to give 580 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3660, 2950, 2860, 1740, 1710, 1455, 1440, 1380, 1360, 1325, 1285, 1270, 1250, 1195, 1180, 1135, 1080, 1040, 1025, 980, 920, 875 cm^{-1};

NMR ($CDCl_3$ solution):δ; 8.40 (2H, s), 5.95–5.20 (4H, m), 5.15–4.55 (2H, m), 4.45–3.20 (8H, m), 3.20–2.65 (4H, m);

TLC (developing solvent, methylene chloride - methanol = 19:1);

Rf = 0.23.

EXAMPLE 11

15-[2-(1,3-Dithiacyclohexyl)]-16,17,18,19,20-pentanorprostaglandin-$F_{2α}$

580 mg. of 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoic acid (prepared as described in Example 10) were dissolved in 5.5 ml. of a mixture of acetic acid, water and tetrahydrofuran (65:35:10) and the solution stirred at 40 to 45° C. for 1.5 hours. The reaction mixture was diluted with 50 ml. of ethyl acetate, washed with water and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and n-hexane (2:1) as eluent to give 220 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3680, 3000, 2930, 1730, 1710, 1420, 1380, 1285, 1250, 1175, 1120, 1050, 975, 915, 870 cm^{-1};

NMR ($CDCl_3$ + DMSO-d_6 solution):δ; 5.73–4.16 (4H, m), 4.78 (4H, broad s), 4.39–3.70 (4H, m), 3.10–2.55 (4H, m);

TLC (developing solvent, chloroform - tetrahydrofuran - acetate acid = 10:2:1);

Rf = 0.11;

Optical Rotation: $[\alpha]_D^{23}$ = +44.4° (c=1.0, $CHCl_3$).

EXAMPLE 12

Methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate

1.04 g. of methyl 9α-acetoxy-11α,15α,-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 16) were dissolved in 15 ml. of absolute methanol and the solution stirred with 300 mg. of potassium carbonate at 40 to 45° C. for 2 hours. The reaction mixture ws then poured into a chilled mixture of dilute hydrochloric acid and ethyl acetate and extracted with ethyl acetate. The organic extracts were washed with an aqeuous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pessure to give 782 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3460, 2945, 1740, 1455, 1440, 1380, 1360, 1325, 1285, 1250, 1200, 1185, 1160, 1130, 1080, 1040, 1020, 980, 920, 875 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.80–5.05 (4H, m), 5.05–4.45 (2H, m), 4.45–3.10 (11H, m), 3.10–2.60 (4H, m);

TLC (developing solvent, benzene - ethyl acetate = 2:1);

Rf = 0.39.

EXAMPLE 13

Methyl 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate

Under an atmosphere of nitrogen, 2 ml. of dimethyl sulphide were added to a solution of N-chlorosuccini-

mide in 20 ml. of toluene and the solution stirred for 10 minutes at 0° C. and then for 1 hour at −24° C. A solution of 595 mg. of methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate (prepared as described in Example 12) in 20 ml. of toluene was added dropwise to the reaction mixture at −50° C. and stirred for 2 hours at −25° C. A solution of 2 ml. of triethylamine in 2 ml. of n-pentane was added to the mixture, which was then diluted with diethyl ether and stirred for 10 minutes. The reaction mixture was diluted with ethyl acetate, washed successively with chilled hydrochloric acid, water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ehtyl acetate (7:1) as eluent to give 547 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 2940, 1745, 1455, 1440, 1380, 1360, 1330, 1250, 1200, 1160, 1130, 1080, 1040, 1025, 980, 920, 875 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.85–5.20 (4H, m), 4.90–4.50 (2H, m), 4.35–3.25 (10H, m), 3.05–2.47 (5H, m);

TLC (developing solvent, benzene - ethyl acetate = 2:1);

Rf = 0.61.

EXAMPLE 14

15-[2-(1,3-dithiacyclohexyl)]-16,17,18,19,20-pentanor-PGE_2 methyl ester

547 mg. of methyl 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-15-[2-(1,3,-dithiacyclohexyl)]-16,17,18,19,20-pentanorprosta-cis-5,trans-13-dienoate (prepared as described in Example 13) were dissolved in 5.5 ml. of a mixture of acetic acid, water and tetrahydrofuran (65:35:10) and the solution stirred at 40° to 45° C. for 1.5 hours. The reaction mixture was then diluted with 50 ml. of ethyl acetate, washed with water and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and n-hexane (1:1) as eluent to give 234 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3400, 3000, 2950, 2900, 1740, 1440, 1370, 1320, 1285, 1255, 1160, 1085, 1035, 975, 915, 880 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.83–5.65 (2H, m), 5.50–5.26 (2H, m), 4.48–4.28 (1H, m), 4.28–3.38 (2H, m), 3.66 (3H, s), 3.23 (3H, s), 3.00–2.55 (5H, m);

TLC (developing solvent, chloroform - tetrahydrofuran - acetic acid = 10:2:1);

Rf = 0.40.

REFERENCE EXAMPLE 17

2-n-Butyl-1,3-dithiane

30 ml. of a 1.6M solution of n-butyllithium in n-hexane were added dropwise to a solution of 4.8 g. of 1,3-dithiane in 150 ml. of tetrahydrofuran under an atmosphere of nitrogen at −20° to −25° C. After 2 hours stirring, 6 g. of n-butyl bromide in 60 ml. of tetrahydrofuran were added dropwise to the reaction mixture, which was stirred for 1 hour at −20° to −25° C. and for a further 30 minutes at room temperture and then concentrated under reduced pressure. The residue was dissolved in diethyl ether, washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 6.8 g. of the title compound having the following physical characteristics:

IR ($CHCl_3$ solution):ν: 2960, 2940, 2860, 1465, 1430, 1385, 1280, 1240, 1180, 915 cm^{-1};

NMR ($CDCl_3$ solution):δ; 4.04 (1H, t), 3.30–2.50 (4H, m), 0.90 (3H, t),

REFERENCE EXAMPLE 18

Methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate

6.9 ml. of a 1.6M solution of n-butyllithium in n-hexane were added dropwise to a solution of 1.76 g. of 2-n-butyl-1,3-dithiane (prepared as described in Reference Example 17) in 30 ml. of tetrahydrofuran under an atmosphere of nitrogen at −20° to −25° C. and the reaction mixture was stirred at the same temperature for 2 hours. The reaction mixture thus obtained was added dropwise at −78° C. to a solution of 3.1 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 8) in 50 ml. of tetruhydrofuran and the reaction mixture was stirred at the same temperture for 1 hour. Then 2 ml. of acetic acid were added to the reaction mixture, which was concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with water, an aqueous solution of sodium chloride and an aqueous solution of sodium bicarbonate, dried over sodium sulphate and concentrated under reduced pessure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (4:1) as eluent to give 2.01 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3450, 2940, 2860, 1740, 1440, 1380, 1325, 1250, 1135, 1080, 1030, 975, 920 cm^{-1};

NMR ($CDCl_3$ solution):δ; 6.00–5.65 (2H, m), 5.65–5.21 (2H, m), 5.21–4.90 (1H, m), 4.90–4.41 (2H, m), 3,68 (3H, s), 3.20–2.60 (4H, m.), 2.05 (3H, s), 0.90 (3H, t);

TLC (developing solvent, benzene - ethyl acetate = 2:1);

Rf = 0.58.

REFERENCE EXAMPLE 19

Methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13dienoate

19 mg. of p-toluenesulphonic acid and 4 ml. of 2,3-dihydropyran were added to a solution of 4.97 g. of methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 18) in 200 ml. of methylene chloride and the reaction mixture was stirred at room temperaure for 20 minutes, diluted with ethyl acetate, washed with an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromotography on silica gel using a mixture of benzene and ethyl acetate (5:1) as eluent to give 4.2 g. of the title compound having the following physical characteristics:

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IR (liquid film):ν; 2940, 2860, 1740, 1660, 1455, 1440, 1380, 1360, 1330, 1250, 1200, 1185, 1160, 1140, 1125, 1080, 1040, 1025, 980, 920, 875, 820, cm^{-1};
NMR ($CDCl_3$ solution):δ; 6.10–5.49 (2H, m), 5.49–5.19 (2H, m), 5.19–4.25 (4H, m), 4.25–3.18 (8H, m), 2.04 (3H, s).

EXAMPLE 15

Methyl
9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate

A solution of 4.2 g. of methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate (prepared as described in Reference Example 19) in 40 ml. of methanol was stirred with 1.0 g. of potassium carbonate at 40° to 45° C. for 1 hour. The reaction mixture was poured into a chilled mixture of dilute aqueous hydrochloric acid and diethyl ether and extracted with ethyl acetate. The extracts were washed with an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (5:1) as eluent to give 3.11 g. of the title compound having the following physical characteristics:
IR (liquid film)-ν; 3460, 2950, 2870, 1745, 1665, 1460, 1440, 1360, 1330, 1285, 1270, 1250, 1200, 1190, 1160, 1140, 1120, 1080, 1030, 980, 920, 880, 820 cm^{-1};
NMR ($CDCl_3$ solution):δ; 6.00–5.20 (4H, m) 5.10–4.33 (3H), m), 4.33–3.22 (9H, m);
TLC (developing solvent, benzene - ethyl acetate = 2:1).
Rf = 0.52.

EXAMPLE 16

Methyl
9α,11α,15α-Trihydroxy-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate
[16,16-(1,5-Dithiapentano)-$PGF_{2\alpha}$ methyl ester]

1.0 g. of methyl 9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate (prepared as described in Example 15) were dissolved in a mixture of 2 ml. of tetrahydrofuran and 20 ml. of a 65% aqueous solution of acetic acid and the reaction mixture was stirred at 40° to 45° C. for 2 hours and then extracted with ethyl acetate. The extracts were washed with water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dired over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (2:1) as eluent to give 382 mg. of the title compound, having the following physical characteristics, and 190 mg. of the 15β-hydroxy isomer:
IR (liquid film):ν; 3400, 3000, 2950, 2930, 2860, 1740, 1660, 1435, 1370, 1320, 1280, 1250, 1175, 1100, 1060, 1030, 975 cm^{-1};
NMR ($CDCl_3$ solution):ν; 5.90–5.60 (2H, m), 5.60–5.25 (2H, m), 4.60–4.40 (1H, m) 4.30–3.80 (2H, m), 3.16 (3H, s), 2.70–2.11 (7H, m);
TLC (developing solvent, ethyl acetate);
Rf = 0.44; (Rf of the 15β-hydroxy isomer = 0.53),
Optical Rotation: $[\alpha]_D^{23}$ = +44.8° (c=1, $CHCl_3$).

EXAMPLE 17

Methyl
9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate

2.0 ml. of dimethylsulphide were added to a solution of 1.6 g of N-chlorosuccinimide in 50 ml. of toluene at −25° C. After stirring for 1 hour, a solution of 1.7 g. of methyl 9α-hydroxy-11α,15(ξ)-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate (prepared as described in Example 15) in 30 ml. of toluene was added and the reaction mixture was stirred at −25° C. for 2 hours. Then a solution of 3.0 ml. of triethylamine in 5 ml. of n-pentane was added to the reaction mixture, which was stirred at the same temperature for 5 minutes and at room temperature for a further 30 minutes, diluted with 20 ml. of diethyl ether and extracted with ethyl acetate. The extracts were washed with chilled aqueous hydrochloric acid, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (7:1) as eluent to give 1.4 g. of the title compound having the following physical characteristics:
IR (liquid film):ν; 2940, 2860, 1745, 1715, 1455, 1440, 1415, 1380, 1360, 1330, 1250, 1200, 1160, 1130, 1080, 1040, 1025, 980, 915, 875, 820 cm^{-1};
TLC (developing solvent, benzene - ethyl acetate = 2:1);
Rf = 0.66.

EXAMPLE 18

Methyl
9-oxo-11α,15α,-dihydroxy-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate
[16,16-(1,5-Dithiapentano)-PGE_2 methyl ester]

1.4 g. of methyl 9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano-prosta-cis-5,-trans-13-dienoate (prepared as described in Example 17) were dissolved in a mixture of 3 ml. of tetrahydrofuran and 30 ml. of a 65% aqueous solution of acetic acid and the reaction mixture was stirred at 40° to 45° C. for 2 hours, diluted with ethyl acetate, washed with water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (5:2) as eluent to give 6.3 mg. of the title compound, having the following physical characteristics, and 275 mg. of the 15β-hydroxy isomer:
IR (liquid film):ν; 3400, 3000, 2950, 2930, 2860, 1740, 1440, 1380, 1320, 1285, 1250, 1160, 1080, 1050, 980 cm^{-1};
NMR ($CDCl_3$ solution):δ; 6.00–5.75 (2H, m), 5.52–5.28 (2H, m), 4.68–4.48 (1H, m), 4.28–3.92 (1H, m), 3.67 (3H, s), 3.30–2.54 (7H, m);
TLC (developing solvent, benzene - ethyl acetate = 2:3); p0 Rf = 0.36; (Rf of the 15β-hydroxy isomer = 0.44),
Optical Rotation: $[\alpha]_D^{23}$ = −47.0° (c=1, $CHCl_3$).

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REFERENCE EXAMPLE 20

1α-Acetoxy-2α-(6-methoxycarbonylhexyl)-3β-(2-formylethyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane

1.0 g. of 5% palladium of carbon was suspended in 50 ml. of methanol and after the air in the apparatus was replaced by hydrogen, a solution of 1.95 g. of 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-vinyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 8) in 10 ml. of methanol was added thereto. Catalytic reduction of the compound was carried out at room temperature under ambient pressure for 1 hour. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 1.925 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 2940, 2855, 2730, 1740, 1440, 1380, 1330, 1255, 1200, 1180, 1140, 1085, 1040, 980, 925, 910, 880, 820 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.35–4.95 (1H, m), 4.78 –4.35 (1H, m), 4.25–3.20 (6H, m), 10.0–9.80 (1H, broad s);

TLC (developing solvent, benzene - ethyl acetate = 2:1);

Rf = 0.62.

REFERENCE EXAMPLE 21

Methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16,16-(1,5-dithiapentano)-prostanoate

4.3 ml. of a 1.5M solution of n-butyllithium in n-hexane were added dropwise to a solution of 1.05 g. of 2-n-butyl-1,3-dithiane (prepared as described in Reference Example 17) in 14 ml. of tetrahydrofuran under an atmosphere of nitrogen at −° C. to −25° C. and the reaction mixture was stirred at the same temperature for 2 hours. The reaction mixture thus obtained was added dropwise at −78° C. to a solution of 1.925 g. of 1α-acetoxy-2α-(6-methoxycarbonylhexyl-3β-(2-formyl-ethyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 20) in 20 ml. of tetrahydrofuran and the reaction mixture was stirred at the same temperature for 1 hour. Then 1 ml. of acetic acid was added to the reaction mixture, which was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (8:1) as eluent to give 1.5 g. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3450, 2930, 2850, 1740, 1440, 1380, 1250, 1200, 1175, 1135, 1080, 1030, 980, 920, 875, 815 cm^{-1};

NMR ($CDCl_3$ solution);δ; 5.30–4.93 (1H, m), 4.80–4.40 (1H, m), 4.35–3.25 (7H, m), 3.25–2.53 (4H, m), 2.05 (3H, s), 0.90 (3H, t);

TLC (developing solvent, benzene - ethyl acetate = 3:1); Rf = 0.57.

REFERENCE EXAMPLE 22

Methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prostanoate

By proceeding as described in Reference Example 19 but replacing the methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate by 2.2 g. of methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16,16-(1,5-dithiapentano)-prostanoate (prepared as described in Reference Example 21) dissolved in 20 ml. of methylene chloride and utilising 8 mg. of p-toluenesulphonic acid and 0.7 ml. of 2,3-dihydropyran there were obtained, without purification by column chromatography, 2.5 g. of the title compound, having the following physical characteristics:

IR (liquid film):ν; 2940, 2850, 1740, 1450, 1440, 1380, 1360, 1325, 1250, 1200, 1160, 1135, 1080, 1040, 975, 910, 875 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.36–4.40 (3H, m), 4.40 –3.20 (9H, m);

TLC (developing solvent, benzene - ethyl acetate = 4:1); Rf = 0.60.

EXAMPLE 19

Methyl 9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prostanoate

By proceeding as described in Example 15 but replacing the methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate by 2.5 g. of methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prostanoate (prepared as described in Reference Example 22) dissolved in 30 ml. of methanol and stirred with 200 mg. of potassium carbonate at 45° to 50° C. for 1.5 hours, and using a mixture of benzene and ethyl acetate (7:1) as eluent there were obtained 889 mg. of the title compound having the following physical characteristics:

IR (liquid film):ν; 3530, 2940, 2850, 1740, 1650, 1625, 1480, 1455, 1440, 1380, 1360, 1330, 1280, 1250, 1200, 1180, 1160, 1135, 1080, 1035, 990, 915, 875, 820 cm^{-1};

NMR ($CDCl_3$ solution):δ; 5.10–4.50 (2H, m), 4.40–3.23 (10H, m);

TLC (developing solvent, benzene - ethyl acetate = 4:1); Rf = 0.40.

EXAMPLE 20

Methyl 9α,11α,15(ξ)-trihydroxy-16,16-(1,5-dithiapentano)prostanoate [16,16-(1,5-Dithiapentano)-13,14-dihydro-15(ξ)-$PGF_{1\alpha}$methyl ester]

By proceeding as described in Example 18, but replacing the methyl 9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate by 423 mg. of methyl 9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prostanoate (prepared as described in Example 19) and utilising a mixture of 1 ml of tetrahydrofuran and 10 ml. of a 65% aqueous solution of acetic acid, and using a mixture of cyclohexane and ethyl acetate (2:1) as eluent there were obtained 280 mg. of

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the title compound having the following physical characteristics:

IR (liquid film):ν; 3430, 2940, 2850, 1740, 1440, 1285, 1260, 1200, 1180, 1120, 1080 cm^{-1};

NMR ($CDCl_3$ solution):δ; 4.45–3.80 (3H, m), 3.65 (3H, s), 3.30–2.60 (7H, m);

TLC (developing solvent, benzene - ethyl acetate = 2:3); Rf = 0.41.

EXAMPLE 21

Methyl 9α-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prostanoate

0.5 ml. of dimethylsulphide was added to a solution of 400 mg. of N-chlorosuccinimide in 15 ml. of toluene at −25° C. and the solution was stirred at −20° to −25° C. for 1 hours. To the solution thus obtained, a solution of 465 mg. of methyl 9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropranyloxy)-16,16-(1,5-dithiapentano)-prostanoate (prepared as described in Example 19) in 10 ml. of toluene was added and the reaction mixture was stirred at −25° C. for 2 hours. Then a solution of 1 ml. of triethylamine in 1.5 ml. of n-pentane was added to the reaction mixture, which was stirred at room temperature for 10 minutes, diluted with 10 ml. of diethyl ether, stirred for a further 10 minutes, and then diluted with ethyl acetate. The mixture was then washed successively with chilled dilute aqueous hydrochloric acid, chilled water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (8:1) as eluent to give 346 mg. of the title compound having the following physical characteristics.

IR (liquid film): ν; 2930, 2850, 1740, 1710, 1450, 1435, 1375, 1355, 1325, 1280, 1245, 1200, 1160, 1135, 1080, 1035, 980, 915, 870, 815 cm^{-1};

NMR ($CDCl_3$ solution): δ; 5.00–4.42 (2H, m), 4.42–3.20 (9H, m);

TLC (developing solvent, benzene - ethyl acetate = 4:1); Rf = 0.49.

EXAMPLE 22

Methyl 9-oxo-11α,15(86)-dihydroxy-16,16-(1,5-dithiapenanto)prostanoate [16,16-(1,5-Dithiapentano)-13,14-dihydro-15(ξ)-PGE_1 methyl ester]

By proceeding as described in Example 18 but replacing the methyl 9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)-prosta-cis-5,trans-13-dienoate by 346 mg. of methyl 9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16,16-(1,5-dithiapentano)prostanoate (prepared as described in Example 21) dissolved in a mixture of 1 ml. of tetrahydrofuran and 10 ml. of a 65% aqueous solution of acetic acid, stirring the reaction mixture at 40° to 45° C. for 1.5 hours, and using a mixture of cyclohexane and ethyl acetate (2:1) as eluent there were obtained 240 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3430, 2940, 2850, 1740, 1455, 1440, 1420, 1380, 1330, 1285, 1245, 1200, 1175, 1120, 1080, 1050, 1020 cm^{-1};

NMR ($CDCl_3$ solution): δ; 4.40–3.80 (2H, m), 3.65 (3H, s), 3.20–2.58 (7H, m);

TLC (developing solvent, benzene - ethyl acetate = 2:3); Rf = 0.49.

REFERENCE EXAMPLE 23

Methyl 9α,11α,15(ξ)-trihydroxy-16-oxo-prostanoate [16-Oxo-13,14-dihydro-15(ξ)-$PGF_{1\alpha}$ methyl ester]

Under an atmosphere of nitrogen, a solution of 280 mg. of 16,16-(1,5-dithiapentano)-13,14-dihydro-15(ξ)-$PGF_{1\alpha}$ methyl ester (prepared as described in Example 20) in 5 ml. of acetonitrile was added dropwise at 0° C. to a solution of 243 mg. of N-chlorosuccinimide and 348 mg. of silver nitrate in a mixture of 10 ml. of acetonitrile and 4 ml. of water. After stirring for 25 minutes, 1 ml. of dimethyl sulphoxide was added to the reaction mixture, which was then stirred for 30 minutes at room temperature. The reaction mixture was extracted with a mixture of ethyl acetate and diethyl ether (1:2). The extracts were washed with a saturated aqueous solution of ammonium chloride, water and an aqueous solution of sodium chloride, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (1:1) as eluent to give 74 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3400, 2920, 2840, 1735, 1710, 1640, 1460, 1450, 1435, 1360, 1260, 1200, 1170, 1115, 1070, 1040 cm^{-1};

NMR ($CDCl_3$ solution): δ; 4.28–3.75 (3H, m), 3.64 (3H, s), 2.78 (3H, broad s), 2.47 (2H, t), 2.29 (2H, t);

TLC (developing solvent, benzene - ethyl acetate = 2:3); Rf = 0.21.

REFERENCE EXAMPLE 24

Methyl 9,16-dioxo-11α,15(ξ)-dihydroxy-prostanoate [16-oxo-13,14-dihydro-15(ξ)-PGE_1 methyl ester]

Proceeding as described in Reference Example 23, but replacing the 16,16(1,5-dithiapentano)13,14-dihydro-15(ξ)-$PGF_{1\alpha}$ methyl ester by 240 mg. of 16,16-(1,5-dithiapentano)-13,14-dihydro-15(ξ)-PGE_1 methyl ester (prepared as described in Example 22) dissolved in 5 ml. of acetonitrile, utilising a solution of 243 mg. of N-chlorosuccinimde and 348 mg. of silver nitrate in a mixture of 10 ml. of acetonitrile and 4 ml. of water and using a mixture of cyclohexane and ethyl acetate (5:2) as eluent there were obtained 63 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3430, 2930, 2850, 1740, 1640, 1435, 1400, 1360, 1245, 1200, 1170, 1120, 1075 cm^{-1};

NMR ($CDCl_3$ solution): δ; 4.35–3.95 (2H, m), 3.63 (3H, s), 3.03–2.58 (3H, m), 2.48 (2H, t), 2.28 (2H, t);

TLC (developing solvent, benzene - ethyl acetate = 2:3); Rf = 0.44.

REFERENCE EXAMPLE 25

Methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-15(ξ)-hydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate

By proceeding as described in Reference Example 9 but utilising the reaction mixture obtained from 2.35 ml. of a 1.4M solution of n-butyllithium in n-hexane and a solution of 0.491 ml. of phenylthiomethylthio-methane (prepared as described in Reference Example 1) in 6 ml. of tetrahydrofuran and replacing the 1α-acetoxy-2α-(6-methoxycarbonylhex-cis-2-enyl)-3β-(2-formyl-trans-

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vinyl)-4α-(2-tetrahydropyranyloxy)cyclopentane by 700 mg. of 1α-acetoxy-2α-(6-methoxycarbonylhexyl)-3β-(2-formyl-ethyl)-4α-(2-tetrahydropyranyloxy)-cyclopentane (prepared as described in Reference Example 20) dissolved in 12 ml. of tetrahydrofuran and stirring the reaction mixture at −70° C. for 1.5 hours and at room temperature for 20 minutes, and using a mixture of benzene and ethyl acetate (6:1) as eluent there were obtained 400 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3450, 1740, 1590, 1440, 1260, 1030 760 cm^{-1};

NMR ($CDCl_3$ solution): δ; 60–7.00 (5H, m) 5.20–4.85 (1H, m), 4.70–4.35 (1H, m), 3.63 (3H, s), 2.22 (1.5H, s), 2.12 (1.5H, s), 2.02 (3H, s).

REFERENCE EXAMPLE 26

Methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-prostanoate

By proceeding as described in Reference Example 10 but utilising 0.1 ml. of 2,3-dihydropyran and a small amount of p-toluenesulphonic acid, replacing the methyl 9α-acetoxy-11α,15α-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate by 255 mg. of methyl 9α-acetoxy-11α-(2-tetrahydropyranyloxy)-16(ξ)-hydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate (prepared as described in Reference Example 25)dissolved in 3 ml. of methylene chloride and using a mixture of benzene and ethyl acetate (15:1) as eluent there were obtained 200 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 1740, 1590, 1440, 1250, 1030, 760 cm^{-1};

NMR ($CDCl_3$ solution: δ; 7.60–7.00 (5H, m), 5.15–4.80 (1H, m) 4.80–4.40 (2H, m), 3.62 (3H, s), 2.25 (1.5H, s), 2.20 (1.5H, s), 2.02 (3H, s).

EXAMPLE 23

Methyl 9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-prostanoate

By proceeding as described in Example 3 but replacing the methyl 9α-acetoxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5, trans-13-dienoate by 200 mg. of methyl 9α-acetoxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate (prepared as described in Reference Example 26) dissolved in 3 ml. of methanol, utilising 50 mg. of anhydrous potassium carbonate and purifying the product by column chromatography on silica gel using a mixture of benzene and ethyl acetate (5:1) as eluent there were obtained 147 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 3450, 1740, 1590, 1440, 1030, 760 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.60–7.00 (5H, m), 4.80–4.40 (2H, m) 3.62 (3H, s), 2.24 (1.5H s), 2.20 (1.5H, s).

EXAMPLE 24

Methyl 9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate

By proceeding as described in Example 4 but utilising 0.152 ml. of dimethylsulphide and 117 mg. of N-chlorosuccinimide in 3.7 ml. of toluene, replacing the methyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprosta-cis-5,trans-13-dienoate by 110 mg. of methyl 9α-hydroxy-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate (prepared as described in Example 23) dissolved in 1.5 ml. of toluene and utilising a solution of 0.217 ml. of triethylamine in 0.31 ml. of n-pentane there were obtained, without purification by column chromatography, 90 mg. of the title compound having the following physical characteristics:

IR (liquid film): ν; 1740, 1710, 1590, 1440, 1030, 760 cm^{-1};

NMR ($CDCl_3$solution): δ; 7.60–7.00 (5H, m), 4.80–4.40 (2H, m), 3.62 (3H, s), 2.24 (1.5H, s), 2.20 (1.5H, s).

EXAMPLE 25

Methyl 9-oxo-11α,15(ξ)-dihydroxy-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate [16(ξ)-Phenylthio-16-methylthio-17,18,19,20-tetranor-13,14-dihydro-15(ξ)-PGE_1 methyl ester]

90 mg. of methyl 9-oxo-11α,15(ξ)-bis-(2-tetrahydropyranyloxy)-16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranorprostanoate (prepared as described in Example 24) were dissolved in a mixture of 0.35 ml. of tetrahydrofuran and 2.25 ml. of a 65% aqueous solution of acetic acid and the reaction mixture was stirred at 40° C. for 1.5 hours, poured into water and extracted with ethyl acetate. The extracts were washed with an aqueous solution of sodium bicarbonate, water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and cyclohexane (1:3) as eluent to give 42 mg. of the title compound having the following physical characteristics:

TLC (developing solvent, ethyl acetate - cyclohexane = 5:1); Rf = 0.50;

IR (liquid film): ν; 3400, 1740, 1590, 1440, 760 cm^{-1};

NMR ($CDCl_3$ solution): δ; 7.59–7.25 (5H, m), 4.25–3.95 (2H, m), 3.90–3.70 (1H, m), 3.67 (3H, s), 3.20–2.50 (3H, m), 2.27 (1.5H, s), 2.26 (1.5H, s).

The present invention includes within its scope pharmaceutical compositions which comprise at least one new thereapeutically useful compound of general formula VI, or cyclodextrin clathrate or non-toxic salt thereof, together with a pharmaceutical carrier or coating. In clinical practice the new compounds of the present invention will normally be administered orally, vaginally, rectally or parenterally.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules. In such solid compositions one or more of the active compounds is, or are, admixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, or lactose. The compositions may also

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comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate. Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing one or more of the active substances with or without the addition of diluents or excipients.

Solid compositions for vaginal administration inlcude pessaries formulated in manner known per se and containing one or more of the active compounds.

Solid compositions for rectal administration include suppositories formulated in manner known per se and containing one or more of the active compounds.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also include adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorportion of sterilising agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage for the therapeutic effect desired shall be obtained. Obviously several unit dosage forms may be administered at about the same time. In general, the preparations should normally contain at least 0.025% by weight of active substance when required for administration by injection; for oral administration the preparations will normally contain at least 0.1% by weight of active substance. The dose employed depends upon the desired therapeutic effect, the route of administration and the duration of the treatment.

In the adult, the doses per person are generally between 0.01 and 5 mg. by oral administration in the treatment of hypertension, between 0.5 and 100 μg. by oral administration in the treatment of gastric ulceration, and between 0.001 and 50 mg. by oral, intravaginal, intravenous and extra-amniotic administration for contraception and menstrual regulation in female mammals and in the termination of pregnancy and the induction of labour in pregnant female mammals.

Prostaglandin compounds according to the present invention may be administered orally by any method known per se for administration by inhalation of drugs which are not themselves gaseous under normal conditions of administrtion. Thus, a solution of the active ingredient in a suitable pharmaceutically-acceptable solvent, for example water, can be nebulized by a mechanical nebulizer, for example a Wright Nebulizer, to give an aerosol of finely-divided liquid particles suitable for inhalation. Advantageously, the solution to be nebulized is diluted, and aqueous solutions containing from 1 to 100 μg., and more particularly 10 to 50 μg., of active ingredient per ml. of solution are particularly suitable. The solution may contain stabilizing agents such as sodium bisulphite and buffering agents to give it an isotonic character, e.g. sodium chloride, sodium citrate and citric acid.

The active ingredients may also be administered orally by inhalation in the form of aerosols generated from self-propelling pharmaceutical compositions. Means for producing self-propelling compositions for generating aerosols for administration as medicaments are, for example, described in detail in U.S. Pat. Nos. 2,868,691 and 3,095,355.

The following Example illustrates pharmaceutical compositions according to the invention.

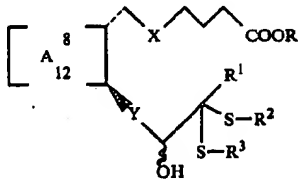
EXAMPLE 26

16(ξ)-Phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 methyl ester (2 mg.) was dissolved in ethanol (10 ml.), mixed with mannitol (18.5 g.), sieved through a 30-mesh sieve, dried at 30° C. for 90 minutes and again sieved through a 30-mesh sieve. Aerosil (microfine silica; 200 mg.) was added and the powder obtained was machine-filled into forty No. 2 hard gelatin capsules to give capsules each containing 50 μg. of 16(ξ)-phenylthio-16-methylthio-17,18,19,20-tetranor-PGE_2 methyl ester which after swallowing of the capsules is released into the stomach.

We claim:

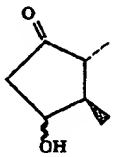
1. A compound of the formula:

VI

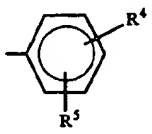


wherein A represents a grouping of the formula:

VIIB



x represents ethylene, Y represents trans-vinylene, R represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms, R^1 represents a hydrogen atom or a straight- or branched-chain alkyl groups containing from 1 to 10 carbon atoms, R^2 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, R^3 represents a grouping of the formula:



wherein R^4 and R_5 each represents a hydrogen or halogen atom, a trifluoromethyl group or an alkyl group containing from 1 to 3 carbon atoms and cyclodextrin

03/03/2003, EAST Version: 1.03.0002

clathrates of such acids and esters and, when R represents a hydrogen atom, non-toxic salts of such acids.

2. A compound according to claim 1 wherein R represents a hydrogen atom or a methyl group.

3. A compound according to claim 1 wherein R_1 represents a hydrogen atom or a straight- or branched-chain alkyl group of 1 to 4 carbon atoms.

4. A compound according to claim 1 wherein R^2 represents a straight- or branched-chain alkyl group of from 1 to 4 carbon atoms and R^3 represents a phenyl group.

5. A compound according to claim 1 which is 16(ξ)-phenylithio-16-methylthio-17,18,19,20-tetranor-PGE_1 methyl ester.

* * * * *

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TABLE 1-continued

Receptor Binding and Single Dose Activity

Compound	Substituents on 19-nortestosterone[#]				Androgenic Activity[##]				
					Seminal	Ventral	Levator	Estrogen	Estrogenic
RIT No.	7α	11β	Other	Androgen RBA*	Vesicles	Prostate	Ani	RBA**	Activity[$]
				(n = 4)					
1471-032	CH_3	CH_3	5-alpha-dihydro		377	742			0.7
1471-034	CH_3	CH_2=		176	993	1519–2148			
1471-038	H	CH_3	delta-14	11	100***	<100***	400***		

[#]Estr-4-en-17β-ol-3-one
*Relative binding (Dihydrotestosterone = 100) to androgen receptor from rat ventral prostate
[##]Subcutaneous administration to immature castrated male rats (Testosterone = 100)
**Relative binding (Estradiol = 100) to estrogen receptor from immature female rat uterus
[$]Subcutaneous administration to immature female rats (Estradiol = 100)
***Single dose level study

TABLE 2

Long Term Androgenic Activity in Male Rats
(% Change from Control)

Compound	Substituents on 19-nortestosterone			Week after Dose	Final Body Weight (%) change from control)	Seminal Vesicle Weight (% change from control)	Ventral Prostate Weight (% change from control)
	7α	11β	Other				
Testosterone enanthate (0.6 mg)			10-CH_3-Enanthate ester	1	0%	452%	409%
				2	6%	318%	339%
				4	-7%	281%	291%
				6	0%	248%	405%
				8	-6%	187%	150%
				10	0%	179%	130%
RTI 1471-029 (0.3 mg)	CH_3	CH_3	Enanthate ester	1	9%	571%	368%
				2	1%	580%	582%
				4	3%	438%	583%
				6	-1%	603%	649%
				8	-10%	312%	340%
				10	-2%	426%	562%
(0.6 mg)				1	15%	968%	628%
				2	6%	1428%	778%
				4	1%	1222%	1145%
				6	0%	1777%	1810%
				8	-16%	1044%	858%
				10	1%	924%	749%

The compounds of the present invention may be used in any formulation which is suitable for administration by oral, buccal, nasal, intravenous, dermal, subdermal, intramuscular or rectal means. However, the present compounds may be advantageously used in smaller than conventional skin patches, in formulations for buccal administration or in aerosol form. When used in aerosol form, the compounds of the present invention may be used in compressed air or other gaseous medium suitable for nasal injection in a can or vial having spraying means, such as a nozzle, for releasing the contents. Such containing means and aerosol formulations for nasal administration are known in the art.

The compounds and/or compositions of the present invention when formulated for dermal application may be in the form of a cream, lotion or solution for facile topical application. In preparing the cream, lotion or solution, any conventional and dermatologically acceptable base formulation may be used.

For example, a base formulation may be prepared in accordance with any of U.S. Pat. Nos. 4,126,702; 4,760,096 or 4,849,425, all of which are incorporated herein by reference in the entirety.

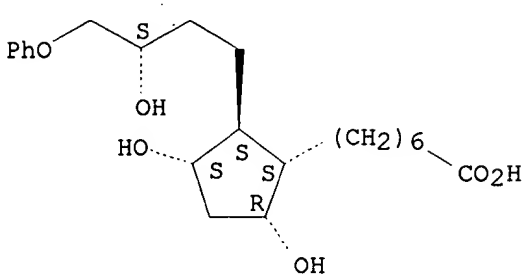
The present compounds and/or compositions of the present invention may be used alone or in combination with one or more other pharmacologically active compound as noted above for hormone treatment of a mammal in either human or animal use.

Further, the present compounds and/or compositions of the present invention may also be used alone or in combination with progestins or gonodotrophin-releasing hormone analogs, either agonists or antagonists, in controlling male fertility. In either utility, the amount administered per dosage is generally from about 5% to about 125% of a conventional dosage of a conventional drug. The male may be a human or an animal, such as a cat, dog, pig, cow, sheep or ox.

In accordance with the present invention, while the dosages of the present compounds and/or compositions admin-

L3 1 ANSWERS REGISTRY COPYRIGHT 2004 ACS on STN
IN Cyclopentaneheptanoic acid, 3,5-dihydroxy-2-(3-hydroxy-4-phenoxybutyl)-, [1.alpha.,2.beta.(R*),3.alpha.,5.alpha.]- (9CI)
MF **C22 H34 O6**

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

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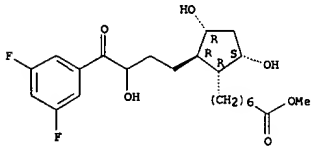
L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **54347-92-1** REGISTRY

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:628114 CAPLUS
DOCUMENT NUMBER: 133:222497
TITLE: Preparation of prostaglandin F analogs for treatment of bone disorders and glaucoma
INVENTOR(S): Delong, Mitchell Anthony; Soper, David Lindsey; Wos, John August; De, Biswanath
PATENT ASSIGNEE(S): The Procter & Gamble Company, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051979	A1	20000908	WO 2000-US5299	20000229
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NZ 513826	A	20010928	NZ 2000-513826	20000229
EP 1159265	A1	20011205	EP 2000-914785	20000229
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008778	A	20011218	BR 2000-8778	20000229
JP 2002538138	T2	20021112	JP 2000-602207	20000229
AU 763715	B2	20030731	AU 2000-36130	20000229
AU 2000036130	A5	20000921		
US 6451859	B1	20020917	US 2001-914531	20010829
NO 2001004240	A	20011102	NO 2001-4240	20010831

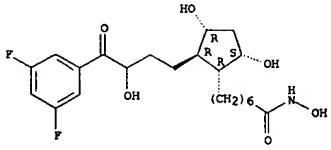
PRIORITY APPLN. INFO.: US 1999-122929P P 19990305
WO 2000-US5299 W 20000229
OTHER SOURCE(S): MARPAT 133:222497
AB The prostaglandin F analogs I (R = CO2H, C(O)NHOH, CO2R2, CH2OH, S(O)R2, C(O)NHR2, C(O)NHS(O)2R2, or tetrazole where R2 = alkyl, heteroalkyl, carbocyclic or heterocyclic aliph. ring, monocyclic arom. or heteroarom. ring; R3 = lower alkyl or heteroalkyl, haloalkyl; preferred R2 = Me, Et, CHMe2; X = CH=C=CH, CH=CH, CH=N, C(O), C(O)Y where Y = O, S, NH; Z = arom. or heteroarom. ring provided that when Z is a heteroarom. ring Z is attached via a carbon atom) and all stereoisomers, or a pharmaceutically acceptable salt or biohydrolyzable amide, ester or imide of these analogs were prepd. Thus II (no data) was prepd. in a multistep sequence starting from Me 7-[3(R)-hydroxy-5-oxo-1-cyclopenten-1-yl]heptanoate. These compds. are useful in the treatment and prevention of bone disorders with the preferred dosage for systemic administration of about 1 to 50 .mu.g/kg body wt. per day. Pharmaceutical compns. contg. I are described.
IT **291530-95-5P 291531-01-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



IT **291530-97-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of prostaglandin F analogs for treatment of bone disorders and glaucoma)
RN 291530-97-7 CAPLUS
CN Cyclopentaneheptanamide, 2-[4-(3,5-difluorophenyl)-3-hydroxy-4-oxobutyl]-N,3,5-trihydroxy-, (1R,2R,3R,5S)- (9CI) (CA INDEX NAME)

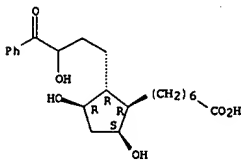
Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

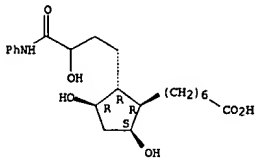
L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(prepn. of prostaglandin F analogs for treatment of bone disorders and glaucoma)
RN 291530-95-5 CAPLUS
CN Cyclopentaneheptanoic acid, 3,5-dihydroxy-2-(3-hydroxy-4-oxo-4-phenylbutyl)-, (1R,2R,3R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 291531-01-6 CAPLUS
CN Cyclopentaneheptanoic acid, 3,5-dihydroxy-2-[3-hydroxy-4-oxo-4-(phenylamino)butyl]-, (1R,2R,3R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **291530-96-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of prostaglandin F analogs for treatment of bone disorders and glaucoma)
RN 291530-96-6 CAPLUS
CN Cyclopentaneheptanoic acid, 2-[4-(3,5-difluorophenyl)-3-hydroxy-4-oxobutyl]-3,5-dihydroxy-, methyl ester, (1R,2R,3R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$C_{22}H_{34}O_6$